STUDIES ON FORMULATION AND CHARACTERIZATION OF ACYCLOVIR SUSTAINED RELEASE MATRIX TABLETS BY USING NATURAL POLYMERS

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Submitted by

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CERTIFICATE

This is to certify that the research work entitled "**STUDIES ON FORMULATION AND CHARACTERIZATION OF ACYCLOVIR SUSTAINED RELEASE MATRIX TABLETS BY USING NATURAL POLYMERS''** submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment for the award of the Degree of the Master of Pharmacy (Pharmaceutics) was carried out by **L.LAKSHMIKANDTH (Register No. 26116007)** in the Department of Pharmaceutics under my direct guidance and supervision during the academic year 2012-2013.

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CERTIFICATE

This is to certify that the dissertation entitled **"STUDIES ON FORMULATION AND CHARACTERIZATION OF ACYCLOVIR SUSTAINED RELEASE MATRIX TABLETS BY USING NATURAL POLYMERS"** the confide research work carried out by **L.LAKSHMIKANDTH (Register No. 26116007)** in the Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, Melmaruvathur which is affiliated to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, under the guidance of **Mr.K.SUNDARAMOORTHY,** B.Sc., M.Pharm., Professor, Department of Pharmaceutics, Adhiparasakthi College of Pharmacy, during the academic year 2012-2013.

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Dedicated

To

My beloved Parents

&Teachers...

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L.LAKSHMIKANDTH

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ABBREVIATIONS

%	----	Percentage
<	----	Less Than
>	----	More Than
°C	----	Degree Celsius
µg	----	Microgram
µg/ml	----	microgram per milliliter
ADME	----	Absorption, Distribution, Metabolism, Excretion
AUC	----	Area Under Curve
BP	----	British Pharmacopoeia
CAS	----	Chemical Abstract Service
CC	----	Carr's Compressibility Index
cm	----	Centimeter
CNS	----	Central Nervous System
CMV	----	Cyto-megalo virus
DSC	----	Differential Scanning Calorimeter
DDS	----	Drug Delivery System
DNA	----	Deoxyribo Nucleic Acid
ER	----	Extended Release
EP	----	European Pharmacopeia
F	----	Formulation
FTIR	----	Fourier Transform-Infra Red Spectroscopy
GIT	----	Gastrointestinal Tract

GSK	----	GlaxosmithKlene
HSV	----	Herpes Simplex Virus
gm	----	Grams
g/cm^3	----	gram per centimeter cube
HCl	----	Hydrochloric acid
HIV	----	Human immunodeficiency virus
hrs	----	Hours
ICH	----	International Conference on Harmonization
IP	----	Indian Pharmacopoeia
kg/cm^2	----	kilogram per centimeter
KBr	----	Potassium Bromide
LSC	----	Loose surface crystal
M	----	Molarity
mg	----	Milligram
ml	----	Milli liter
mm	----	Millimeter
MW	----	Molecular Weight
Mp	----	Melting point
N	----	Normality
nm	----	Nanometer
N.M.T	-----	Not More Than
NDDS	----	Novel Drug Delivery System
PBS	----	Phosphate Buffer Solution

pH	----	Negative logarithm of hydrogen ion
Pka	----	Dissociation constant
RH	----	Relative Humidity
RNA	----	Ribo Nucleic Acid
rpm	----	Revolutions per Minute
S. No.	----	Serial Number
S.D.	----	Standard deviation
SR	----	Sustained Release
T	----	Time
TBD	----	Tapped bulk density
USP	----	United State Pharmacopoeia
USPNF	----	United State Pharmacopoeia and National Formulary
UV-VIS	----	Ultraviolet-Visible
Vs	----	Versus
W/v	----	weight/volume
λ	----	Wavelength
λ_{max}	----	Absorption maximum

INTRODUCTION

1. INTRODUCTION

1.1 SUSTAINED RELEASE DRUG DELIVERY SYSTEM *(Bankar G.S and Rhodes C.T., 2009; Brahmankar D.M and Jaiswal S.B., 2005; Chein Y.W., 2002)*

The goal of a sustained release dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended and specified period of time. This is generally accomplished by attempting to obtain "zero-order" release from the dosage form. Zero-order release constitutes drug release from the dosage form which is independent of the amount of drug in the delivery system (i.e. a constant release rate). Sustained-release systems generally do not attain this type of release and usually try to mimic zero-order release by providing drug in a slow first-order fashion (i.e., concentration release dependent). Systems that are designated as prolonged release can also be considered as attempts at achieving sustained-release delivery.

The term “Controlled- release drug product” has been used to describe various types of oral extended release rate dosage forms, including sustained release (SR), sustained action, prolonged action, long action, and retarded release. These terms for extended release dosage forms were introduced by drug companies to reflect a special design for producing an extended release (ER) dosage form or used as a marketing term In the last two-three decades interest in sustain release drug delivery systems is remarkably increasing. This has been due to various factors .

- Developing new drug entities.
- Expiration of international patents
- Discovery of new polymeric materials suitable for prolonging the drug release.
- Need of therapeutic efficacy and safety achieved by sustained release drug delivery.

The subject of sustain release has been reviewed by various authors. Several books have been published on it. These reviews and books provide not only the mechanisms and technology of production of dosage forms but also the information on clinical evidence and performance.

There are many definitions of sustained release but the simplest definition is "Any drug or dosage form or medication that prolongs the therapeutic activity of drug''. The overall objective is that, once the drug-carrier material has been injected or otherwise implanted or taken orally into the body, the drug is released at a predetermined rate for some desired period of time. Controlled release technology is relatively new field and as a consequence, research in this field has been extremely fertile and has produced many discoveries.

Non-immediate release delivery systems may be divided conveniently into 4 categories,

A. Sustained release

a) Controlled release

b) Prolonged release

B. Delayed release

C. Site- specific release

D. Receptor release

Sustained- release systems includes any drug delivery system that achieves slow release of drug over an extended period of time

Delayed – release systems are those that use repetitive, intermittence dosing of a drug from one or more immediate release units incorporated into a single dosage forms to make delayed action. Example: Repeat- action tablets and capsules, enteric coated tablets where timed release achieved by a barrier coating..

Controlled release systems are those systems which are successful maintaining constant drug levels in blood or target release (i.e.) release rate of drug occurs in controlled manner.

Prolonged released systems only extends the duration of action and drug release that achieved by conventional drug delivery.

Site specific and receptor release refers to targeting of drug directly to a certain biological location. In the case of site- specific release, the target is a certain organ or tissue, for receptor release, the target is the particular receptor for a drug within an organ or tissue.

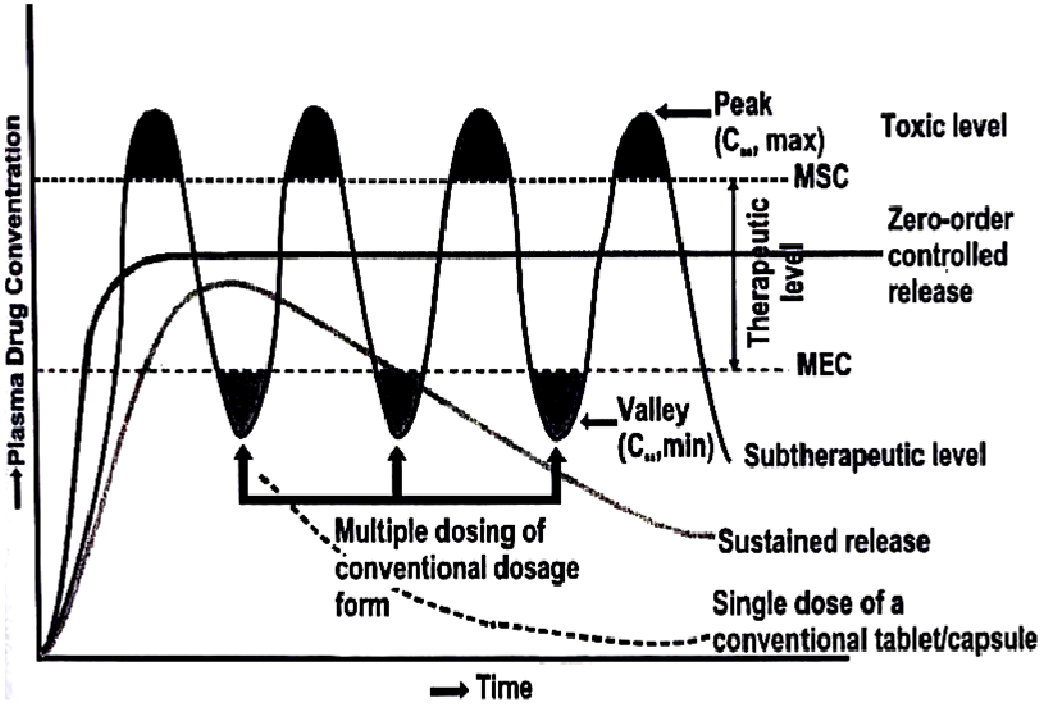


Figure.1 Plasma concentration Vs time profile from conventional multiple and single doses of sustained release drug delivery formulations.

Control release system differs from Sustain release system which simply prolongs the drug release and hence plasma drug levels for an extended period of time (i.e. not necessarily at a predetermined rate). Thus the chief objective of most products should be controlled delivery to reduce dosing frequency to an extent that once daily dose is sufficient for therapeutic management through a uniform plasma concentration at steady state.

1.1.1 Advantages of sustained release drug delivery system *(Bankar G.S and Rhodes C.T., 2009; Chein Y.W., 2002)*

Some advantages are as follows

1. Reduction in dosing frequency.
2. Reduction in GI irritation and other side effects.
3. Avoidance of night time dosing.
4. Reduced fluctuation in circulating drug levels.
5. Increased patient convenience and compliance.
6. More uniform effect.
7. Maximum utilization of drug.
8. Reduction in health care cost through improved therapy.
9. Improve bioavailability of some drugs.

1.1.2 Disadvantages sustained drug delivery system

1. Decreased systemic availability in comparison to immediate release conventional dosage form.
2. Poor *in vitro-in vivo* correlation.
3. Higher cost of formulation.
4. Possibility of dose dumping.
5. Retrival of drug is difficult in case of toxicity, poisoning, or hypersensitivity reactions.

1.2 FUNDAMENTALS FOR A DRUG TO BE SUITABLE FOR DESIGN OF ORAL SUSTAINED RELEASE DOSAGE FORM *(Bandyopadhyay A .K., 2008)*

Some characteristics make a drug more suitable for extended release dosing, such as-

1. Moderate unit dose
2. Elimination half-life between 2 to 8 hours.
3. Broader therapeutic index.
4. Significant extent of absorption in GIT.
5. Minimal first-pass clearance.
6. Optimum solubility characteristics

1.3 FACTORS INFLUENCING OF SUSTAINED RELEASE PRODUCTS

(Bandyopadhyay A .K., 2008)

Oral sustained release drug delivery is the most widely utilized route of administration among all the routes that have been explored for the systemic delivery of drugs via various pharmaceutical products in different dosage forms. Irrespective of their mode of delivery (immediate, sustained or controlled release) and the design of dosage forms (either solid or liquid) they must be developed within the intrinsic characteristics of GIT physiology. A number of variables such as drug properties, route of delivery, target sites, duration of therapy, the disease state and patient variables must be considered. The formulation and performance of sustained release products are greatly influenced by the physicochemical and biological properties of drug.

1.4 PROPERTIES RELEVANT TO SUSTAINED RELEASE DRUG FORMULATIONS *(Banker G.S and Rhodes C.T., 2009; Robinson J.R and Lee V.H.L., 1987)*

During design of sustained release delivery systems, variables such as the route of drug delivery, the type of delivery system, the disease being treated, the patient, the length of therapy and the properties of the drug, are considered. These properties are classified as,

A) Physicochemical and

B) Biological properties

These properties have the greatest effect on the behavior of the drug in the delivery system and in the body. There is no clear-cut distinction between these two categories since the biological properties of a drug are a function of its physicochemical properties. By definition, physicochemical properties are those that can be determined from *in vitro* experiments and biological properties will be those that result from typical pharmacokinetic studies of the absorption, distribution, metabolism, and excretion (ADME) characteristics of a drug and those resulting from pharmacological studies.

A) Physicochemical Properties

a) Dose Size

b) Aqueous Solubility and pKa

c) Partition Coefficient

d) Drug Stability

e) Molecular Size and Diffusivity

f) Drug Protein Binding

B) Biological Properties

a) Absorption

b) Distribution

c) Metabolism

d) Elimination and Biological Half-Life

e) Margin of Safety (Toxicity).

A. Physiochemical properties

a) Dose size: For orally administered drugs, there is an upper limit to the bulk size of the dose to be administered. In general, a single dose of 0.5 – 11.0 gm for conventional dosage form is considered maximal.

b) Aqueous Solubility: Extremes in aqueous solubility are under desirable in the preparation of a SR product. For drug with low water solubility, it will be difficult to incorporate into a SR formulation. The lower limit of solubility for such product has been reported to be 0.1 mg/ml.

c) Partition Co-efficient: drug that are very lipid soluble or water soluble i.e. extremes in partition co-efficient, will demonstrate either low flux in to the tissues or rapid flux followed by accumulation in the tissues. Both extremes are undesirable for a SR system E.g.: Phenothiazines class of compounds is highly lipid soluble.

d) Drug Solubility: since most oral SR systems, by necessity are designed to release their contents over much of the length of the GIT, drugs which are unstable in the environment of the intestine might be difficult to formulate into prolonged release systems.

E.g.: Propanthdine and Probanthine.

B. Biological properties

a) Absorption: Drugs that are slowly absorbed or absorbed with variable absorption rate are poor candidates for SR systems. For oral dosage forms the lower limit on the absorption rate constant is in the range of 0.17 to 0.23 hr^{-1}(assuming GI transit time of 8-12 hr^{-1}).

b) Metabolism: Drugs that are significantly metabolized, especially in region of small intestine, can show decreased bioavailability from SR dosage forms, because less total drug is presented to enzymatic process during a specific period. This allows more complete conversion of drug to its metabolite.

c) Therapeutic Index: Drugs with a narrow therapeutic range which require precise control over the blood levels of the drug are unsuitable for SR dosage forms.

d) Half Life: The biological half life and duration of action of drug obviously plays a major rule in considering a drug for SR systems. Drugs with a very short half life (>2 hr) require large amounts of drug to maintain sustained effects and drugs with longer life (<8hrs) because their effects are already sustained.

1.5 POLYMERS USED IN SUSTAINED RELEASE PHARMACEUTICAL DOSAGE FORMS *(Jain N.K., 2008)*

Polymers are complex and giant molecules known as macromolecules consisting of many repeating units and are formed by process called as polymerization. In general, polymers Can be classified into 3 categories as follows

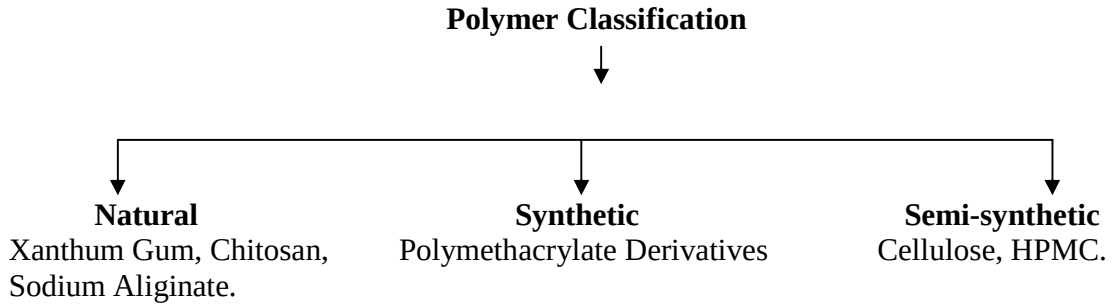


Table1. Classification of Polymers used in Oral Sustained Release Drug Delivery Systems according to their characteristics.

S. No.	Polymer Characteristics	Material
1.	Insoluble, inert	Polyethylene, Polyvinyl chloride, Methyl acrylates-methacrylate copolymer.
2.	Insoluble, erodible	Carnauba wax, Stearyl alcohol, Stearic acid, Polyethylene glycol. Castor wax, Polyethylene glycol, Monostearate triglycerides.
3.	Hydrophilic	Methylcellulose (400cps, 4000cps), Hydroxypropylmthylcellulose (HPMC), Sodium alginate, Galactomannose.

1.6 PRINCIPLE BEHIND SUSTAINED DRUG RELEASE *(Bankar G.S and Rhodes C.T., 2009; Brahmankar D.M and Jaiswal S.B., 2005; Robinson J.R and Lee V.H.L., 1987)*

Dissolution and diffusion controlled systems have classically been of primary importance in oral delivery of medication because of their relative ease of production and cost compared with other methods of sustained or controlled delivery.

The classification of such systems is as follows:

1. Diffusion controlled systems.
2. Dissolution controlled systems.
3. Dissolution and Diffusion controlled systems.
4. Osmotically controlled systems.
5. Ion exchange systems.

1. Diffusion Controlled Systems

Diffusion systems are characterized by the release rate being dependent on its diffusion through an inert membrane barrier. Usually this barrier is an insoluble polymer. In general two types of sub classes of diffusion systems are recognized they are

a. Reservoir devices.

b. Matrix devices.

a. Reservoir devices

Reservoir devices are characterized by a core drug reservoir surrounded by a polymeric membrane..

Advantages

1. Zero order delivery is possible.
2. Release rate variable with polymer type.

Disadvantages

1. Potential toxicity if system fails.
2. System must be physically removed from implant sites.
3. Difficult to deliver high molecular weight compounds.
4. Generally increased cost per dosage units.

b. Matrix Devices

It contains of drug dispersed homogeneously throughout a polymer matrix. In this model, drug in the outside layer exposed to bath solution is dissolved first and then diffuses out of the matrix. The following equation describe the rate of release of drug dispersed in an inert matrix system have been derived by Higuchi.

$Dm/d_h = Cod_h - Cs/2.$

Where, dm = Change in the amount of drug released per unit area.

d_h = Change in the thickness of the zone of matrix that have been depleted of drug.

Co = Total amount of drug in unit volume of matrix.

Cs = Saturated concentration of drug within the matrix.

Advantages

1. Can deliver high molecular weight compounds.
2. Easier to produce than reservoir devices.

Disadvantages

1. Removal of remaining matrix is necessary for implanted systems.
2. Cannot obtain zero order release.

Diffusion Rate Modifications

Modification of the following will change the rate of diffusion

(a) Thickness of the separating layer,

(b) Porosity

(c) Partition coefficient,

(d) Modification of the diffusion co-efficient.

(e) Modification of efficient molecular size.

(f) Modification of viscosity.

(g) Modification of concentration.

2. Dissolution-controlled Systems

Drug with a slow dissolution rate will demonstrate sustaining properties, since the release of the drug will be limited by rate of dissolution. This being the case, SR preparations of drugs could be made by decreasing their dissolution rate. This includes preparing appropriate salts or derivatives, coating the drug with a slowly dissolving material, or incorporating it into a tablet with a slowly dissolving carrier.

The dissolution process at steady state, is described by Noyes-Whitney equation,

$$dc/dt = K_D A(Cs-C) = D/h\ A(Cs-C)$$

Where,

dc/dt = Dissolution rate.

K_D = Diffusion co-efficient

A = surface area of the dissolving solid

Cs = Saturation solubility of the solid.

C = Concentration of solute in bulk solution.

H = Thickness of diffusion layer.

Principles of dissolution rate modification

The following are may affect dissolution rate modification of

(a) Solubility,

(b) Specific area,

(c) Particle shape and surface structure,

(d) Dissolution

(e) Crystallographic modification.

3. Dissolution and Diffusion - Controlled release system

Normally, therapeutic systems will never be dependent on dissolution only or diffusion only. In practice, the dominant mechanism for release will over shadow other processes enough to allow classification as either dissolution rate limited or diffusion controlled.

The mechanism of release from simple erodible slabs, cylinders and spheres has been described by Hopenberg are described as

$$Mt/M = 1 - (1- K_o t/C_o a)^n$$

Where, n = 2 for cylinder and

n = 1 for a slab.

a = Radius of sphere or cylinder or half height of a slab.

M_t = Mass of drug release at time t

M = Mass released infinite time.

Advantages

1. Easier to produce than reservoir devices.
2. Can deliver high – molecular weight compounds.
3. Removal from implant sites is not necessary.

Disadvantages

1. Difficult to control kinetics owning to multiple process of release.
2. Potential toxicity of degraded polymer must be considered.

4. Osmotically controlled systems

This device is fabricated as tablet that contains water soluble osmotically active drug, of that was blended with osmotically active diluents by coating the tablet with a cellulose triacetate barrier which functions as a semi permeable membrane. A laser is used to form a precision orifice in the barrier, through which the drug is released due to development of osmotic pressure difference across the membrane, when this was kept in water.

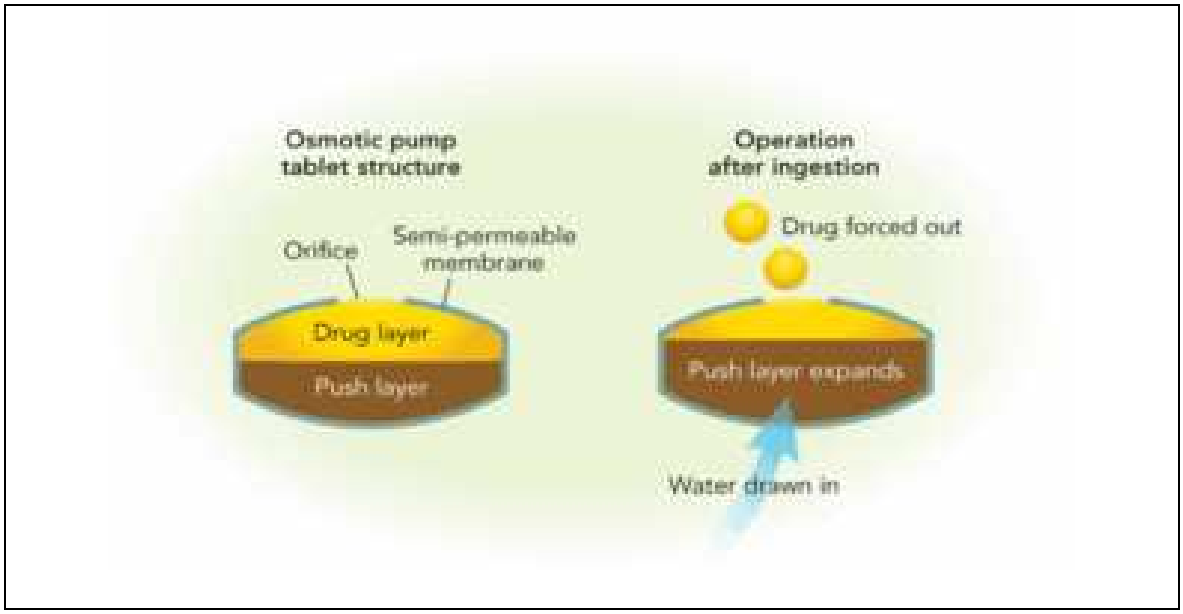


Figure.2 Osmotically controlled release systems.

5. Ion Exchange Systems

These are salts of cationic or anionic exchange resins or insoluble complexes in which drug release results from exchange of bound drug ions that are normally present in GI fluids.

1.7 MATRIX SYSTEMS *(Bankar G.S and Rhodes C.T., 2009; Brahmankar D.M and Jaiswal S.B., 2005; Robinson J.R and Lee V.H.L., 1987)*

- Easy to manufacture
- Versatile, effective, low cost.
- Can be made to release high molecular weight compounds**.**
- Since the drug is dispersed in the matrix system, accidental leakage of the total drug component is less likely to occur, although occasionally, cracking of the matrix material can cause unwanted release.

1.7.1 Different types of Matrix tablets

1) Hydrophilic matrices
2) Hydrophobic matrices
3) Plastic matrices

1) Hydrophilic Matrices

. The matrix tablet may be prepared by direct compression of the blend of active ingredient and certain hydrophilic carriers, or from a wet granulation containing a drug and hydrophilic matrix materials. The hydrophilic matrix requires water to activate the release mechanism and enjoys several advantages, including ease of manufacture and excellent uniformity of matrix tablets. Drug release is controlled by a gel diffusion barrier that is formed and/or tablet erosion. The effect of formulation and processing variables on drug release behavior from compressed hydrophilic matrices has been studied by a number if investigators and can be summarized as follows:

- The matrix building material with fast polymer hydration capacity is the best choice to use in the hydrophilic matrix tablet formulations.

- Generally, reduced particle size of hydrophilic polymer ensures rapid hydration and gel formation, leading to good controlled release.

- For Some hydrophilic matrix building materials, P^H may affect the viscosity of the gel, which forms on the surface, and its subsequent rate of hydration.

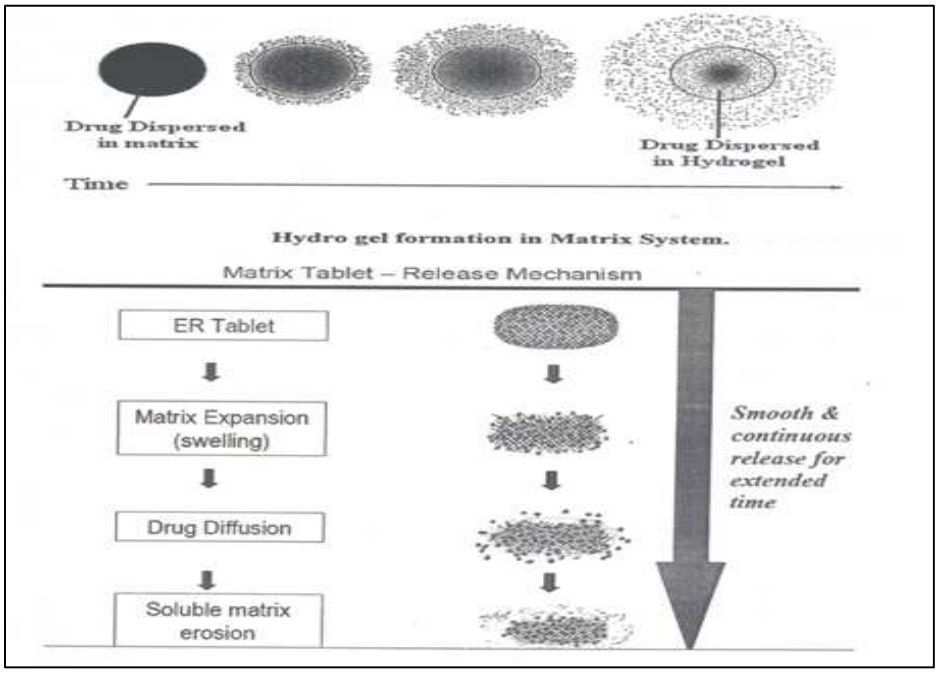


Figure.3 Drug release Mechanism of Matrix tablet.

- Viscosity characteristics of polymers are of great importance in determining the final release properties of the matrix tablet. Generally, the drug release rate is slower for a higher viscosity grade polymer.

- Commonly, water-soluble excipients in the matrix tablet can increase drug release..

2) Hydrophobic Matrices (Fat-Wax matrix tablets)

The drug can be incorporated into a fat-wax granulation by spray congealing in air, blend congealing in an aqueous media with or without the aid of surfactant and spray drying technique. The mixture of active ingredients, waxy materials and fillers can also be converted into granules by compacting with a roller compactor or by direct compression.

Enteric materials such as cellulose acetate phthalate, polyvinyl acetate phthalate, methacrylate copolymers, zein, and shellac may be used to prepare matrix tablets with somewhat a similar release mechanism. The surface erosion of the fat-wax matrix depends upon the nature and percent of fat-wax materials and extenders in the matrix. Other factors such as drug particle size and drug concentration affect release of the drug from the tablet matrix.

3) Plastic Matrix Tablet

. Commonly used plastic materials are polyvinyl chloride, polyethylene, polyvinyl acetate/ vinyl chloride copolymer, acrylate/methyl methacrylate copolymer, ethyl cellulose, cellulose acetate. Plastic matrix tablets, in which the active ingredient in embedded in a tablet with coherent and porous skeletal structure, can be easily prepared by direct compression of the drug with plastic material. Drug solubility in the dissolution medium and in the matrix has the release factors can be summarized as follows:

- The release rate increases as the solubility increases.
- The release rate increases as the drug concentration increases.
- It is possible to modify release rate by inclusion of hydrophilic or hydrophobic additives to the matrix. The decrease in the release rate on addition of hydrophobic substance may be due to decreased wettability of the matrix.
- The release rate from plastic matrix tablets could be decreased by exposure to the acetone vapour without changing the release mechanism.

1.8 FACTORS INFLUENCING SELECTION OF POLYMER

(Rowe R.C., et al., 2003)

Generally rheological behavior and possible interactions with the drug and other components of the dosage form are major factors to be considered. Other factors are,

a) Physicochemical Compatibility

The physicochemical type of polymers and other ingredients in the system must be mutually compatible. Knowledge of charge on the particle surface is helpful in anticipating changes in the stability character.

b) Biological Compatibility

It is obvious that certain polymeric agents will be removed from consideration depending on the route of administration or application. The vulnerability of materials of natural organ to microbiological attack is often cited.

1.9 TABLETS *(Bankar G.S and Rhodes C.T., 2009; Lachman L, et al., 1991)*

Tablets remain popular as dosage forms because they are advantageous to both the manufacturer and the patient.

1.9.1 Advantages of tablet dosage form

- They are a unit dose form**.**
- Their cost is lowest.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.

- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing as embossed or monogrammed punch face.
- They may provide the greatest ease of swallowing.
- They are better suited to large-scale production
- They have the best combined properties of chemical mechanical and microbiologic stability of all the oral forms.

1.9.2 Disadvantages of tablets

- Some drugs resist compression into dense compacts.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract, or any combination of these features may be difficult or impossible to formulate and manufacture as a tablet.
- Bitter – tasting drugs that are sensitive to oxygen or atmospheric moisture may require encapsulation or entrapment prior to compression, or the tablets may require coating. In such cases, the capsule may offer the best and lowest cost approach.

1.9.3 Formulation of tablets

. The first group contains those that help to impart satisfactory processing characteristics to the formulation. These include diluents, binders, glidants and lubricants. The second group of added substances help to give additional desirable physical characteristics to the finished tablet is disintegrants, colors, flavors and sweetening agents and polymers.

Tablet ingredients maybe divided conveniently in to following categories.

- ✓ Diluents
- ✓ Binders.
- ✓ Disintegrants
- ✓ Lubricants and glidants
- ✓ Organoleptic agents.

a) Diluents

In the single dose, the active ingredient in small and an inert substance is added to increase the bulk to make the tablet a practical size for compression like dicalcium phosphate, calcium sulfate, lactose, cellulose, kaolin, etc. Certain diluents such as mannitol, lactose, sorbitol, and inositol, when present in sufficient quantity, disintegration in the mouth by chewing.

b) Binders

Agents used to impart cohesive qualities to the powdered material are referred to as binders or granulators. Materials commonly used as binders include starch, gelatin and sugars such as sucrose, glucose, dextrose, molasses and lactose. Natural and synthetic gums that have been used include acacia, sodium alginate and extract of mucilage, carboxymethyl cellulose, methyl cellulose and polyvinylpyrrolidone.

c) Disintegrant

A disintegrant is added to most tablet formulations a break up or disintegration of the tablet when it contacts water in the gastrointestinal tract.. Tablet fragmentation may be critical to the subsequent dissolution of the drug and to the attainment of satisfactory drug bioavailability. Starch USP and various starch derivatives are the most common disintegrating agents.

d) Lubricants and glidants

Lubricants are included in formulations to reduce wear and friction in the equipment during operation. Some of the lubricants also aid in the enhancing the flow properties of the powders during mixing. Lubricants include calcium stearate, magnesium stearate, mineral oil (light), polyethylene glycol, sodium stearyl fumarate, purified stearic acid, talc, vegetable oil (hydrogenated) and zinc stearate.

Glidants are the substances that improve the flow characteristics of a powder mixture. These materials are always added in the dry state just prior to compression (i.e. during lubrication step). Colloidal silicon dioxide is most commonly used glidants and generally used in low concentration of 1% or less and Talc is also used.

e) Organoleptic agents

The use of colors and dyes in tablet making has served three purposes over the years, distinguishing off- color drugs, product identification, and production of a more elegant product. Flavors are usually limited to chewable tablets or other tablets intended to

dissolve in the mouth.. The use of sweeteners is primarily limited to chewable tablets to exclude or limit the use of sugar in the tablet

1.10. Introduction to Antiviral: *(Don A. Ballington., 2005)*

There are fewer medications to treat viral infections than there are for bacterial infections. Part of the difficulty is that antibiotics often disrupt a cellular process that is unique to the bacterium being treated. This allows dosing of the medication without causing toxicity to the patient. However, because viruses use the cellular processes of the host to function and replicate, medications that block the life cycle of the virus are often toxic to the patient. Thus, the antiviral have been formulated to search and destroy the virus cell lodged in its host cell without interfering with the host cell's normal function. Antiviral are among the drugs of choice for the following conditions. Cytomegalovirus (CMV) retinitis

Genital herpes

Herpes simplex

Herpes simplex keratitis

Herpes zoster (shingles)

Influenza prophylaxis

Organ transplantation

Varicella (chicken pox)

1.11. Viruses and Their Characteristics:

A virus is a minute infection agent which is much smaller than a bacterium. Unlike a bacterium, a virus does not have all the components of a cell and thus it is able to replicate only within a living host cell. Viruses, among the most common infectious agents in

humans, replicate by using the host cells' metabolic processes. A virus can infect a spectrum of cells including animal, plant, or bacteria cells. Most common viruses are spread by one of the following routes.

Direct contact

Ingestion of contaminated food and water

Inhalation of airborne particles

The individual virus particle, a virion, consists of nucleic acid (nucleoid), either deoxyribonucleic acid (RNA) (but not both), and a protein shell (capsid) that surrounds and protects the nucleic acid. Depending on the virus, the capsid may be converted with spikes that attach to the host cell. Binding of the spikes to membrane receptors simulates a process whereby the cell engulfs the virus. A virus without an envelope covering the capsid is called a naked virus.

1.12. Stages of Viral Infection:

Within the body, viral infection takes place at the cellular level and in the following stages.

1. The virus attaches to a cell receptor
2. The cell membrane indents and closes around the virus (endocytosis) and thus the virus penetrates the cell
3. The virus escapes into cytoplasm
4. The virus uncoats, sheds its covering, and presents its DNA or RNA to cell nucleus.

1.13. Viral Classification:

Viral infections are classified in two ways. The first classification is the duration or length of time they have been present in the body as well as their severity. The second classification measures the extent of the infections within the body or the parts of the body that are affected.

1.13.1. Viral Duration and Severity:

With the classification of duration and severity there are three categories: acute, chronic, and slow. An acute viral infection quickly resolves with no latent infection. Examples include the common cold, influenza, and various other respiratory tract infections. A chronic viral infection has a protected course with long periods of remission interspersed with reappearance, such as the herpes virus infection. A slow viral infection maintains a progressive course over months or years, with cumulative damage to body tissue, ultimately ending in the host's death. Examples of this type of destructive viral infection include human immunodeficiency virus (HIV) and diseases affecting the central nervous system (CNS).

1.14. Viral Life Cycle: *(Ilango K., 2005)*

Viral life cycle varies with species, but they all share a general petten can be sequenced as follows:

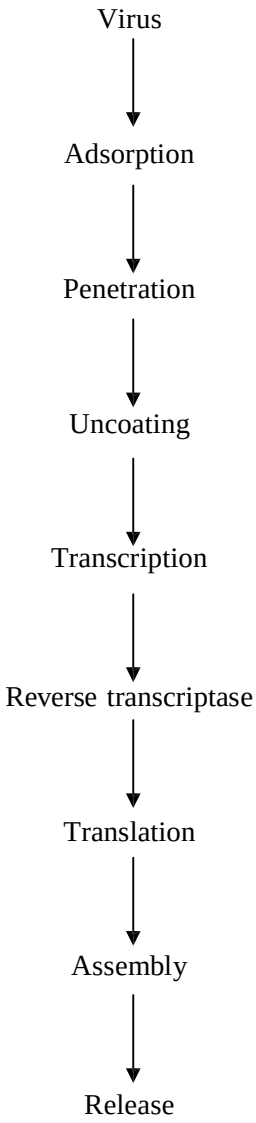


Figure 4: Pathology of viral life cycle

General approaches for treating the virus infection by antiviral agents are:

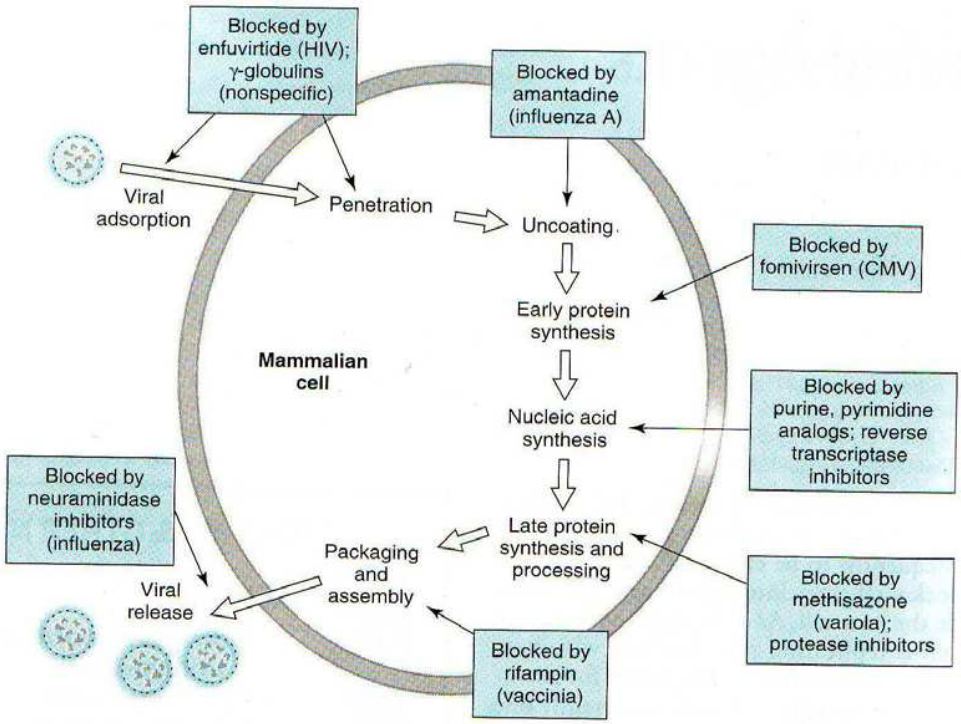


Figure 5: Various classes of anti-viral agents against the virus life cycle

a) Interference of virus attachment to the host

b) Inhibition of virus associated enzymes

c) Inhibition of transcription process

d) Inhibition of translation process

e) Interference with viral regulatory process

f) Interference with glycosylation, phosphorylation, etc.,

g) Interference with viral assembly of viral protein

h) Interference with release of virus from cell surface membrane.

Table 2: List of some RNA virus types together with disease that they cause

RNA Viruses	
Virus	**Disease**
Picornaviruses	Polio, Hepatitis A
Rhinovirus	Commen cold, Pneumonia
Togavirus	Rubella, Encephalitis
Flavirus	Yellow fever, Dengue fever, St.Louis encephalitis
Bunyaviruses	Encephalitis, Hemorrhagic fever
Rhabdoviruses	Vesicular stomatitis
Myxoviruses	Mumps, Measles
Reoviruses or Rotaviruses	Diarrhea
Arenaviruses	Lymphatic choriomeningitis
Retroviruses	Human immunodeficiency syndrome (HIV)

Table 3: List of some DNA virus types together with disease that they cause

DNA Viruses	
Virus	**Disease**
Herpes viruses	Herpes, Cold sores
Papovaviruses	Polyoma, warts
Adenoviruses	Respiratory complications
Poxvirus	Smallpox
Parvirus	Canine distemper

NEED AND OBJECTIVES

2.1 NEED OF THE PRESENT WORK

Herpes simplex virus (HSV) is a member of family of herpes viridae, a DNA virus. There are two types of Herpes Simplex Viruses (HSV). viz HSV type 1 and type 2. HSV type 1 is the herpes virus that is usually responsible for cold sores of the mouth, the so called “fever blisters”. HSV type 2 is the one that most commonly causes genital herpes. The infection causes painful sores on the genitals in both men and women.. Currently the treatments available for herpes simplex are conventional tablets and topical gel for application on outbreaks. The drugs that are commonly used for herpes simplex are Acyclovir, Valaclovir and Famciclovir.

Acyclovir, the first agent to be licensed for the treatment of herpes simplex virus infections, is the most widely used drug for infections such as cutaneous herpes, genital herpes, chicken pox, varicella zoster infections. Acyclovir is currently marketed as capsules (200 mg), tablets (200, 400 and 800 mg) and topical ointment. Oral acyclovir is mostly used as 200 mg tablets, five times a day. In addition, long term administration of acyclovir (6 month or longer) is required in immune compromised to patient with relapsing herpes simplex infection. The presently available conventional therapy is associated with a number of drawbacks such as highly variable absorption and low bioavailability (10–20%) after oral administration. Furthermore, with increase in dose, there is decrease in bioavailability. Moreover, because the mean plasma half life of the drug is 2.5 hours, five times a day administration is required. In order to make oral therapy of acyclovir more patients

compliant there is a need of using different approaches like matrix tablets, nanoparticle and polymeric films.

Among the many techniques used for modulating the drug release profile, the most commonly used method is embedment of the drug into a polymer matrix.

The matrix may be formed by either dissolving or dispersing the drug uniformly in the polymer mass. Such polymer matrices can give

- Desirable release profiles,
- Cost effective manufacturing method and also
- Broad regulatory acceptance.

Hence, in the present work, an attempt is made to develop sustained-release matrix tablets of Acyclovir, with the use of various natural polymers for their sustaining effect. Direct compression technique is used for tablet formulation along with the addition of suitable additives by using of natural polymers of Sodium Alginate and Chitosan.

2.2 THE OBJECTIVES OF THIS STUDY

To design of sustained release matrix tablet of Acyclovir that will help in releasing only small quantities of drug over a prolonged period of time.

- To study the effect of polymers and polymer concentration on release profiles of sustained release matrix tablet of Acyclovir formulations.
- To study the different types of Schemes on release profiles of sustained release matrix tablet of Acyclovir formulations.
- To carry out Concurrent Process validation of the selected process of sustain release matrix tablet of Acyclovir
- To perform stability studies as per ICH guidelines.

PLAN OF WORK

3. PLAN OF WORK

- **Literature survey**.
- **Selection and procurement of suitable drug candidate and excipients.**
- **Pre-formulation studies.**
  - **Characterization of drug**
    - Melting point determination
    - Solubility determination
    - UV spectra (λ_{max})
    - IR spectra
    - Loss on drying
    - Standard carve of Acyclovir
    - Percentage purity of drug
  - **Identification and Drug polymer interaction study.**
    - Fourier transform Infra-Red (FTIR) spectroscopy
    - Differential Scanning Calorimeter (DSC)
  - **Physical Characterization of Powdered blend**
    - Bulk density
    - Tapped density
    - Carr's index
    - Hausner's ratio
    - Angle of repose

- **Formulation of Sustained release matrix tablet of Acyclovir**
- **Evaluation of Sustained release matrix tablet of Acyclovir**
  - Appearance
  - Dimensions (Thickness and Diameter)
  - Hardness
  - Percent friability
  - Weight variation test
  - Drug content of Acyclovir (assay)
  - *In-vitro* dissolution studies
  - Kinetic of *In-vitro* Drug Release
- **Stability studies.**
- **Result and discussion**
- **Summary and conclusion**

REVIEW OF LITERATURE

LITERATURE REVIEW

Basak S.C., *et al.*, (2006): Monolithic matrix tablets of Ambroxol Hydrochloride were formulated as sustained release tablets employing Hydroxy Propyl Methyl Cellulose polymer, and the sustained release matrix tablets containing 75mg Ambroxol hydrochloride were developed using different drug polymer ratios of Hydroxy Propyl Methyl Cellulose.Tablets were prepared by direct compression. Formulation was optimized on the basis of acceptable tablet properties and in vitro drug release.

Chandria M., *et al.*, (2009): The present investigation attempt has been madeincrease therapeutic efficacy, reduce frequency of administration and improve patient Compliance, by developing sustained release matrix tablets of Zidovudine, were developed by using drug polymer ration kollidon SR, HPMC k15M and HPMC K100M as matrix former lubricated formulation were compressed by direct compression and wet granulation method. Compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thinkess, *in-vitro* dissolution, and swelling index, all formulation showed compliance with pharmacopeial standards.

Ghosh S., *et al.*, (2009): The objective of the study was to develop matrix tablets for oral controlled release of Aceclofenac. Matrix tablets of Aceclofenac, using various viscosity of hydrophilic polymer HPMC in two different proportions, hydrophobic polymer ethyl cellulose and Guar gum were prepared by wet granulation method and subjected to *in vitro* drug release studies. The drug release from all HPMC matrix tablets followed various release kinetics, formulation no - F7 followed Higuchi kinetics. Furthermore, the results of

the *in vitro* studies in pH 7.5 phosphate buffer medium showed that F7 tablets provided controlled release comparable with market sustained release formulation (Aeroff-SR tablets).

Kabir A.K.L*, et al.*, (2009): Objective of this study was to develop a sustained release matrix tablet of Acyclovir using hydroxypropyl methylcellulose (HPMC K15M and HPMC K100M CR in various proportions as release controlling factor by direct compression method. The results of dissolution studies indicated that the formulations F-2 and F-3 could extend the drug release up to 24 hours. From this study, a decrease in release kinetics of the drug was observed when the polymer concentration was increased. Kinetic modeling of *in vitro* dissolution profiles revealed the drug release mechanism ranges from diffusion controlled or Fickian transport to anomalous type or non-Fickian transport, which was only dependent on the type and amount of polymer used. The drug release followed both diffusion and erosion mechanism in all cases.

Saptarshi D., *et al.*, (2010): An attempted was to formulate the oral sustained release metformin hydrochloride matrix tablets by using hydroxyl methyl cellulose polymer (HPMC) as

rate controlling factor and to evaluate drug release parameters as per various release kinetic models. It is observed that the basic goal of therapy in the development of metformin hydrochloride release dosage form is to increase bioavailability; reduce risk of hospitalization, deliver drug at a near constant rate for approximately 12hrs; independent of food intact and gastrointestinal p^H. The dry granulation technique was used to compress the tablet as powder showed the poor flowability; wet granulation technique was not selected for the present work.

Soni T., *et al.,* (2008): The development of a meaningful dissolution procedure for drug products with limited water solubility has been a challenge to the pharmaceutical industry. Aceclofenac (BCS Class II drug) is a non steroidal anti-inflammatory drug. There is no official dissolution medium available in the literature. In the present study, parameters such as solubility, medium pH, surfactant type, dissolution behavior of formulations, and influence of sink conditions, stability, and discriminatory effect of dissolution testing were studied for the selection of a proper dissolution medium.

Yadav I.K. *et al.,* (2010): The objective of the present study was to develop the oral sustained release matrix tablets of Aceclofenac using hydrophilic and hydrophobic polymers. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis and its biological half life is 4 hrs. Controlled release formulations of Aceclofenac (200 mg) were prepared by direct compression method. The drug release from optimized formulations F1, F4 and F7 was extended for a period of 12 hrs. The kinetic treatment to optimized formulations showed that the release of drug follows zero order model and Super Case II transport for F1 and F7.

Yeole P.G., *et al.,* (2006): In the present investigation, an attempt has been made to increase therapeutic efficacy, reduce frequency of administration, and improve patient compliance, by developing sustained release matrix tablets of Diclofenac sodium. Sustained release matrix tablets of Diclofenac sodium, were developed by using different drug:polymer ratios, such as F1(1:0:12), F2(1:0:16), F3(1:0:20), F4(1:0:24) and F5(1:0:28). Xanthan gum was used as matrix former, and microcrystalline cellulose as diluents. All the lubricated formulations were compressed using 8mm flat faced punches.

MATERIALS AND EQUIPMENTS

5. MATERIALS

5.1. RAW MATERIAL USED

Table.4: List of raw materials with source

S. No	Name of Ingredients	Name of supplier
1	Acyclovir	Ajanta pharmaceutical limited, Mumbai.
2	Xanthan Gum	Qualigens fine chemicals, Mumbai.
3	Sodium Alginate	Qualigens fine chemicals, Mumbai.
4	Chitosan	Paras Chem suppliers ,Pune, India.
5	Polyvinyl Pyrolidone	Qualigens fine chemicals, Mumbai
6	Magnesium stearate	Qualigens fine chemicals, Mumbai.
7	Starch	Qualigens fine chemicals, Mumbai.
8	Talc	Qualigens fine chemicals, Mumbai.
9	Hydrochloric acid	S d fine-chem limited, Mumbai.
10	Chloroform	Qualigens fine chemicals, Mumbai.
11	Ethanol (95%)	S d fine-chem limited, Mumbai.

5.2. EQUIPMENTS USED

Table.5: List of equipments with model/make

Sr. No	Equipment	Model/ Make
1	Electronic balance	Shimadzu BL-220H.
2	Bulk density apparatus	Indolab VTAP/MATIC-II.
3	Standard sive (20 and 40#)	Jayant scientific, IND.
4	Hot air oven	Chemi Equipments, Bombay.
5	Sixteen punch tablet compression machine	Cadmach, Ahemdabad, india.
6	Friability apparatus	Veego scientific VFT-DV.
7	Hardness tester	Monsanto Hardness tester.
8	Varnier caliper	Indolab, MITUTOYO.
9	Humidity chamber	Labtech.
10	USP tablet dissolution apparatus Type II	Veego scientific VDA-8DR.
11	UV spectrophotometer	Shimadzu-1700 PharmaspecUV-VISIBLE spectrophotometer.
12	FTIR spectrophotometer	Parkin elmer-Pharmaspec-1.
13	Differential scanning calorimeter	Shimadzu DSC 60, Japan.

5.3 DRUG PROFILE

ACYCLOVIR: *(IP., 2007; Merck Index., 1997; USP., 2009; Tripathi K.D., 2004)*

Acyclovir is active against herpes group of virus; H. *simplex* type 1 is the most sensitive followed by the H. *simplex* type II> varicella-zoister =Epstein-bar virus; Cytomegalovirus (CMV) is practically not affected .the prototype antiviral agent used to treat various types of herpes infections. Since, acyclovir was the first antiviral to be considered the gold standard for the treatment of herpes infections, all other anti herpes virus medications are compared to it. It is approved for the prophylaxis of herpes genitals.

A. Chemical name:

9 – [(2 hydroxyethoxy) methyl] -9H- guanine 2-amino-1, 9-dihydro-9-[(2-hydroxyethoxy) methyl]-6H-purin-6-one

B. Structural formula:

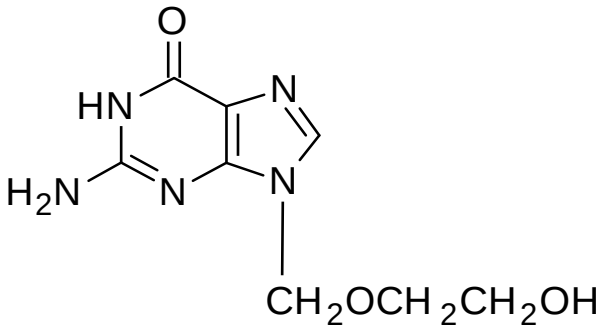


Fig 6: Structure of Acyclovir

C. Physical properties:

Molecular formula : $C_8H_{11}N_5O_3$

Molecular weight : 225

Description : White, crystalline powder, fine powder

Odour : Characteristic

Taste : Bitter to alkaline

Melting point : Melt at about 230º with decomposition (BP)

: Melt at about 250º with decomposition (USP)

Dissociation constant (pKa): 2.3, 9.2

Solubility : Freely soluble in dimethyl sulphoxide;
Slightly soluble in water;
Very slightly in ethanol (95%);
Dissolves in dilute solutions of mineral acids and Alkaline hydroxides.

Storage : Store in well closed containers

D. Mode of action:

Acyclovir is a synthetic analogue deoxy guanosine in which the carbohydrate moiety is acyclic. The modes of action of acyclovir consist of the following consecutive mechanism:

1. Conversion to active acyclovir monophosphate within cells by viral thymidine kinase. This phosphorylation reaction occurs faster in infected cell than normal cell, because acyclovir is a poor substrate for the normal cell thymidine kinase. Acyclovir monophosphate is further converted in to di and triphosphate by a normal cellular enzyme guanosine monophosphate kinase.

2. Acyclovir triphosphate inhibits viral DNA polymerase by competing deoxy guanosine triphosphate. The triphosphate drug is also incorporated in to viral DNA where it acts as a chain terminator, because it has 3' - hydroxy group, like cyclic sugar, 3' 5' - phosphodiester bond can be formed. It acts as suicide inhibitor because the terminated DNA template containing acyclovir as ligand binds irreversibly with DNA polymerase and inactivates. It is a drug of choice in both prophylaxis and treatment of herpes simplex virus.

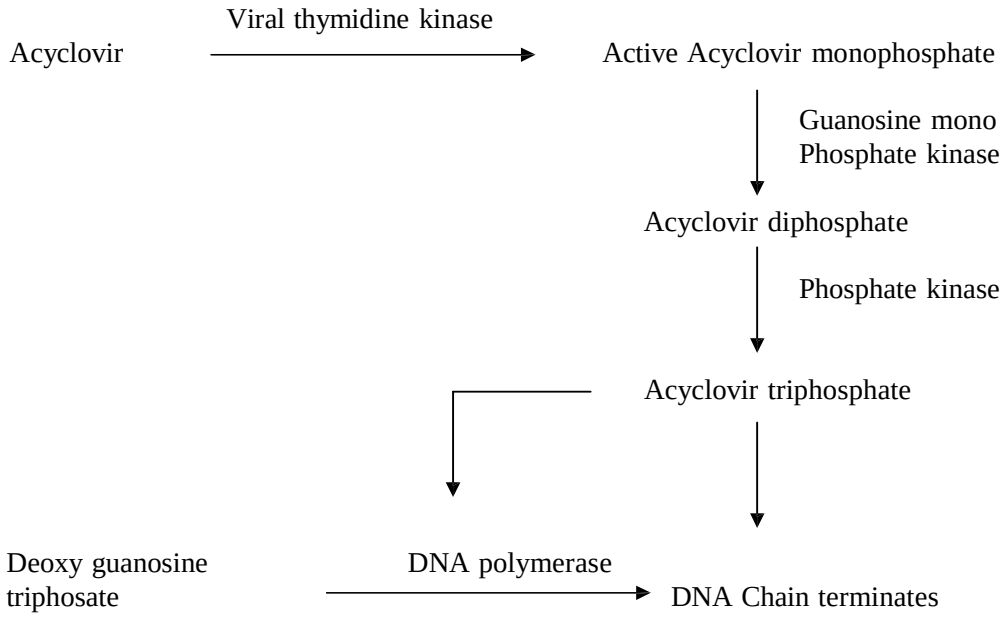


Fig. 7: Mechanism of Acyclovir

E. Pharmacokinetics:

Oral bioavailability	**:** 15-30%
Protein binding	**:** 9-33%
Volume of distribution	**:** 0.8 L/kg.
Half life	**:** 2.5-3.3 hours.

Route of administration **:** Especially oral, IV, cream 5% in an aqueous cream base and eye ointment.

F. Absorption:

Acyclovir is poorly absorbed from the gastro intestinal tract following oral administration. The oral bioavailability ranges from 10 to 20% and decreases with increased doses. The C_{max} and AUC are dose dependent and show no proportionality. The C_{max} for a bioavailability ranges from 10 to 20% and decreases with increased doses. The C_{max} and AUC are dose dependent and show no proportionality. The C_{max} for a 200 mg dose is 0.83 µg/mL, 1.21 µg/mL for a dose of 400 mg and 1.61 µg/mL for a dose of 800 mg. Oral absorption is not affected by food consumption. There is minimal systemic absorption following topical administration of acyclovir. No drug is detectable in the blood or urine. Following intravenous administration of acyclovir, the mean C_{max} is 9.8 µg/mL with a dose of 5 mg/kg every 8 hours and 20.7 µg/mL with a dose of 10 mg/kg every 8 hours.

G. Distribution:

The volume of distribution is 0.8 L/kg. Protein binding of acyclovir ranges from 9% to 33%, and distributes extensively throughout the body. The highest concentrations are in the kidneys, liver and intestines. Cerebro spinal fluid concentrations are about 50% that of the plasma. Acyclovir does cross the placenta.

H. Metabolism:

Acyclovir is converted to acyclovir monophosphate by virus specific thymidine kinase, diphosphate by cellular guanylate kinase, and then ultimately converted to acyclovir triphosphate via cellular enzymes. Acyclovir undergoes minimal hepatic metabolism by aldehyde oxidase, alcohol dehydrogenase, and aldehyde dehydrogenase to form inactive metabolites.

I. Excretion:

Acyclovir is primarily eliminated by the kidneys via glomerular filtration and tubular secretion. It is found in the urine from 62% to 90% as unchanged drug and metabolites. The plasma elimination half life of Acyclovir ranges from 2.5 to 3.3 hours in patients with normal renal function.

J. Contraindications:

Hypersensitivity to valcyclovir, acyclovir, or any component of the formulations.

K. Precautions:

Dosage reduction is recommended when administering acyclovir to patients with renal impairment.

- Use with caution in the elderly due to decreased renal function.
- Use with caution in patients who receive nephrotoxic drugs.
- Use caution when administering via IV in those with pre-existing neurologic abnormalities, serious hepatic or electrolyte abnormalities, or hypoxia.

L. Interactions:

Probenecid: concomitant administration of probenecid and Cimetidine with acyclovir increases the acyclovir mean half life and under the plasma concentration curve, thus decreasing renal clearances of probenecid.

- Observe caution if administration nephrotoxic drugs simultaneous.
- Zidovudine: Acyclovir along with zidovudine causes sever drowsiness and lethargy.

M. Dosage forms:

- Intravenous infusion
- Capsule
- Tablet
- Suspension
- Topical cream
- Topical ointment

N. Dosage limits:

Capsules	**:** 200 mg
Tablets	**:** 400 mg, 800 mg
Suspension	**:** 200 mg/5mL
Powder for injection	**:** 500 mg, 1000 mg
Solution for injection	**:** 50 mg/5mL
Creams	**:** 5%
Ointment	**:** 5%

O. Over dosage Measures:

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 g/mL) is exceeded in the intra tubular fluid. This can be treated with hemo dialysis until renal function is restored.

P. Commercial products of Acyclovir:

Table 6: Commercial products of Acyclovir

Trade name	**Dosage Form**	**Recommended Dosage**	**Manufacturer**
Acivir	Tablet Injection Cream (5 %) Ointment (3 %)	200, 400 and 800 mg 10 mL 5 g 5 g	Cipla
Acivirall	DT- tablet	200 and 400 mg	Finecure
Alovir	Tablet	200, 400 and 800 mg	Adley
Axovir	Tablet Injection	200, 400 and 800 mg 250 and 800 mg vials	Samarth
Clovirax	DT- tablet Cream (5 %)	200, 400 and 800 mg 5 g	Purehealth
Cyclovir	Tablet Cream (5 %)	200 mg 5 g	Zydus cadilla
Herpex	DT- tablet Cream (5 %)	200 and 800 mg 5 g	Torrent
Lovir	Tablet	400 and 800 mg	Eli lilly
Ocuvir	Ointment (3 %)	5 g	FDC
Zovirax	Suspension Ointment (3 %) Tablet	400 mg/5 Ml 5 g 200, 400 and 800 mg	GSK

5.4. POLYMER PROFILE

A) XANTHAN GUM *(Rowe R.C., et.al., 2003)*

Synonyms **:** Corn sugar gum; E415; Xantural; Rhodigel.

Chemical name **:** Xanthan gum.

Molecular Weight **:** 2000000.

Description **:** Cream or white-colored odorless free flowing fine powder.

Structural formula **:**

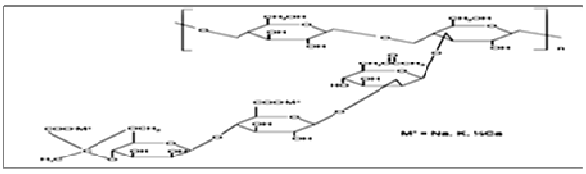


Figure.8 Structure of Xanthan gum

Solubility **:** Practically insoluble in ethanol and ether.

Soluble in cold or warm water.

Viscosity **:** The viscosity of xanthan gum solution is considerably increased or gelation occurs, in the presence of some materials such as ceratonia, guar gum and magnesium aluminium silicate.

Incompatibilities **:** Xanthan gum is an anionic material and is not usually compatible with cationic surfactants as precipitation occurs. Xanthan gum is compatible with most synthetic and natural viscosity increasing agents.

Functional Category : Viscosity increasing agent, suspending agent.

Applications in pharmaceutical formulation:

Xanthan gum is widely used in oral and topical pharmaceutical formulations. It is used as Viscosity increasing agent, suspending agent, and also has been used to prepare sustained release matrix tablets.

Stability and storage conditions:

It is a stable material. The bulk material should be stored in a well closed container in a cool, dry place.

B) SODIUM ALGINATE **(** *Row R.C.,et al., 2003)*

Nonproprietary Names:

BP: Sodium alginate, PhEur: Natrii alginas, USPNF: Sodium alginate

Synonyms:

Algin; alginic acid, sodium salt; E401; Kelcosol; Keltone; Protanal; sodium polymannuronate.

Chemical Name and CAS Registry Number: Sodium alginate [9005-38-3]

Empirical Formula : $(C_6H_7O_6Na)_n$

Molecular Weight: The block structure and molecular weight of sodium alginate samples has been investigated.

Structural Formula:

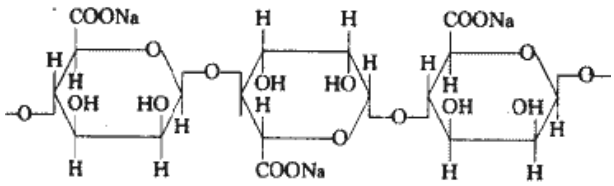


Figure 9: Structure of Sodium Alginate

Functional Category:

Stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent.

Grades:

Various grades of sodium alginate are available yielding aqueous solutions of varying viscosities within a range of 20 to 400 centipoises in 1% solution at 20 °C.

Applications in Pharmaceutical Formulation or Technology:

- Sodium alginate for oral and topical pharmaceutical formulations.
- In tablet formulations, sodium alginate may be used as both a binder and disintegrant, diluents in capsule formulations. Sustained release oral formulations are prepared by using, since it can delay the dissolution of a drug from tablets, capsules and aqueous suspensions. In topical formulations, sodium alginate is mainly used as a thickening and suspending agent in product such as variety of pastes, creams, and gels, and as a stabilizing agent for oil-in-water emulsions
- Recently, sodium alginate has been used mostly for microencapsulation of drugs, in contrast with the more conventional microencapsulation techniques which use organic solvent systems. It has also been used in the formulation of nanoparticles. Other NDDS

containing sodium alginate include ophthalmic solutions that form a gel in situ when administered to the eye.

Description:

Sodium alginate occurs naturally as an odorless and tasteless, white to pale yellowish-brown colored powder.

Typical Properties:

Acidity/alkalinity: pH 7.2 for a 1% w/v aqueous solution

Solubility:

Practically insoluble in ethanol (95%), ether, chloroform, and ethanol/water mixtures in which the ethanol content is greater than 30%. Also, the pH is less than 3. Slowly soluble in water, forming a viscous colloidal solution.

Stability and Storage Conditions:

Sodium alginate is a hygroscopic material, although it is stable if stored at low relative humanities and a cool temperature.

C) CHITOSAN *(Rowe R.C., et al., 2003)*

Synonyms **:** 2-Amino-2-deoxy-(1, 4)-β-D-glucopyranan, deacetylated chitin, deacetylchitin.

Chemical Name **:** Poly-β-(1,4)-2-Amino-2-deoxy-D-glucose.

Molecular Weight **:** Chitosan is commercially available in several types and grades that vary in molecular weight between 10,000 and 10, 00,000 and vary in degree of deacetylation and viscosity.

Structure :

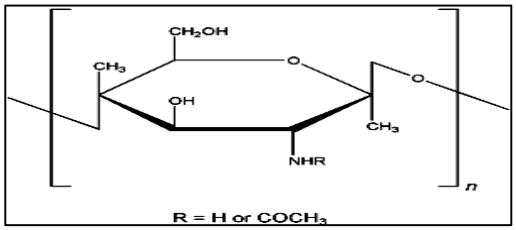


Figure.11 Structure of Chitosan

Description : Chitosan occurs as odorless, white or creamy-powder or flakes. Fibre formation is quite common during precipitation and the chitosan may look cottonlike.

Functional Category : Coating agent, film-forming agent, Mucoadhesive tablet binder and viscosity-increasing agent.

Acidity/Alkalinity : pH = 4.0–6.0 (1% w/v aqueous solution)

Density : 1.35–1.40 g/cm^3

Glass Transition Temperature: 203°C.

Solubility : It is sparingly soluble in water, practically insoluble in ethanol, organic solvents, and neutral or alkali solutions. Chitosan dissolves readily in dilute and concentrated solutions of most organic acids. The solubility is affected by the degree of deacetylation.

Viscosity (dynamic) : A wide range of viscosity types is commercially available.

Chitosan is an excellent viscosity- enhancing agent in an acidic environment.

Applications : It is used as a component of sustained release dosage form & mucoadhesive dosage forms.

Stability and Storage: Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place.

Incompatibilities : Chitosan is a cationic material. Chitosan is incompatible with strong oxidizing agents.

5.5. EXCEPIENTS PROFILE

1) STARCH *(Rowe R.C., et.al., 2003)*

Non-Proprietary name : Maize starch, Potato starch.

Synonym : Amido, Amilo

Incompatibilities : With some drugs which form a complex (complexation reaction) and retain in kidneys as oxalate complexes.

Chemical Name and CAS Registry Number: Starch [9005-25-8]

Chemical Formula **:** [C6H10O5] where n= 300-1000.

Category **:** Glidant, capsule diluents, capsule disintegrant, tablet binder.

Description **:** White to off-white powder comprising very small spherical or ovoid granules.

Solubility **:** Insoluble in cold water and cold ethanol

Stability **:** Dry, unheated starch is stable if protected from high humidity

Storage **:** To be stored in a well closed container, cool and dry place.

Safety **:** Allergic reactions to starch are very rare and individual apparently allergic to one particular starch may not experience adverse effects with a starch from a different botanical sources.

Particle size **:** Corn starch: 2-32 µm; Potato starch: 10-100 µm; Rice starch: 2-20 µm; Wheat starch: 2-45 µm.

Viscosity **:** 13.0 cP for a 2%w/w aqueous dispersion of corn Starch at 25 °C

2) TALC

(Rowe R.C., et.al., 2003)

Synonyms	**:**	French chalk, purified talc, talcum, soapstone
Description	**:**	A very fine, white to grayish white, impalpable, odorless crystalline powder, unctuous, adheres readily to skin, soft to touch and free from granules.
Empirical formula	**:**	$Mg.6\ (Si_2O_5)\ 4(OH)_4$
Functional category	**:**	USP: Tablet and/or capsule lubricant, Glidant and anti caking agent BP: Talc dusting powder Others: Anti adherent
Typical Properties:		
Density	**:**	19-24 Ib/ft
Solubility	**:**	Insoluble in water, organic solvents, cold acids and dilute alkalis
Stability and storage conditions:		Stable, Preserve in a well-closed container
Incompatibilities	**:**	Quaternary ammonium compounds
Safety	**:**	Talc dust exposure in the modern mining process does not appear to be injurious to health. Contamination of tissues with talc is liable to cause granulomas. Talc should not be inhaled. Being unreactive, talc may be considered practically non-toxic on ingestion.

3) MAGNESIUM STEARATE *(Rowe R.C., et.al., 2003)*

Synonyms **:** Metallic stearate, Magnesium salt

Functional Category **:** USP: Tablet and/or capsule lubricant

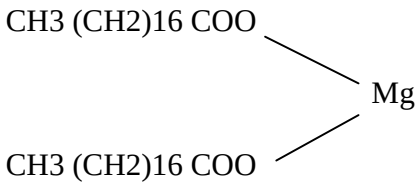
BP/EP: Lubricant; Pharmaceutical

Other: Glidant, Anti-adherent

Empirical Formula **:** C36H70MgO4

Molecular Weight **:** 591.3

Structure **:**



Description **:** It is a fine, white, precipitated or milled, impalpable powder of low bulk density. Odour and taste are slight but characteristic. The powder readily adheres to the skin.

Typical Properties **:**

Solubility **:** Insoluble in water, alcohol and ether. Slightly soluble in hot alcohol and benzene.

Stability and storage conditions: Stable, non-self-polymerizable. Store in a well closed container.

Incompatibilities **:** Acidic substances; alkaline substance; iron salts.

Avoid mixing with strong oxidizing materials. Use with caution with drugs, which are incompatible with alkali.

Safety **:** It is described as an inert or nuisance dust. It is classified as non-hazardous by the department of transportation regulations.

4) POLYVINYL PYROLIDONE (PVP)

Nonproprietary Names **:** None adopted.

Synonym **:** Aminobutyric acid lactam; 4-aminobutyric acid lactam; aminobutyric lactam; minobutyrolactam; butyrolactam; butyrolactam; 2-oxopyrrolidine; *2-Pyrol*; apyrrolidinone; pyrrolidone; a-pyrrolidone; *Soluphor P*.

Chemical Name **:** 2-Pyrrolidinone

CAS Registry Number **:** [616-45-5]

Empirical Formula **:** C_4H_7NO

Molecular Weight **:** 85.11

Description **:** 2-Pyrrolidone occurs as a colorless or slightly colored liquid that solidifies at room temperature and has a characteristic odor.

Functional Category **:** Penetration enhancer; plasticizer; solvent; solubilizing agent.

Applications in Pharmaceutical Formulation or Technology:

Pyrrolidones such as 2-pyrrolidone and *N*-methylpyrrolidone are mainly used as solvents in veterinary injections.1, 2 they have also been suggested for use in human pharmaceutical formulations as solvents in parenteral, oral, and topical applications. In topical applications, pyrrolidones appear to be effective penetration enhancers.1–7 Pyrrolidones have also been investigated for their application in controlled-release depot formulations. Poly-vinyl Pyrrolidone is used in the formulation as plasticizer.

EXPERIMENTAL WORK

6. EXPERIMENTAL WORK

6.1 PREFORMULATION STUDIES

Before the formulation of a product should be investigation of physical and chemical properties of a drug substance alone to effective, stable and safe dosage form. It is the first step in rational development of dosage form.

6.1. Identification of Drug:

The preliminary studies were carried out by testing of different physical and chemical properties of drug as follows.

6.1.1. Organoleptic Properties of Drug: *(Lachman L., 1991)*

The Organoleptic properties like physical state, color, taste, odor etc., of the drug was reported with help of the descriptive terminology. It helps to identify the drug.

6.1.2. Melting Point: *(IP., 2007)*

It is the easy way to identify the drug. The melting point of acyclovir was tested by use of a laboratory melting point apparatus with capillary tube method a procedure given in the Indian Pharmacopeia 2007.

6.1.3. Solubility Profile: *(IP., 2007)*

It is important to know about solubility characteristic of a drug in aqueous system, since they must possess some limited aqueous solubility to elicit a therapeutic response. The solubility of drug was recorded by using various descriptive terminology specified in Indian pharmacopoeia, 2007.

Table 7: Description of solubility

Descriptive term	Parts of solvent required for 1 part of solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble	Greater than or equal to 10,000

6.1.4. UV Spectroscopy (λ max): *(Kuchekar B. S., 2006)*

The absorption maximum of the standard solution was scanned between 200- 400 nm regions on Shimadzu-1700 Pharmaspec UV-visible spectrophotometer. The absorption maximum obtained with the substance being examined corresponds in position and relative intensity to those in the reference spectrum.

6.1.4.1. Development of Standard Curve of Acyclovir in Distilled Water:

(Kuchekar B. S., 2006)

Preparation of Stock Solution of Acyclovir in Distilled Water:

Weighed accurately about 200 mg of Acyclovir was dissolved in little quantity of distilled water and volume was adjusted to 100 ml with the same to prepare standard solution having concentration of 1000 µg/ml. From this solution, pipette out 10 ml and made up to 100 ml with distilled water to produce 100 µg/ml.

Procedure:

From the stock solution, aliquots of 0.4, 0.8, 1.2, 1.6 and 2 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with distilled water to get 4 to 20 µg/ml. Absorbance values of these solutions were measured against blank (Distilled water) at 252 nm using UV-visible spectrophotometer.

6.1.4.2. Development of Standard Curve of Acyclovir in 0.1N HCl:

Preparation of 0.1N HCl:

0.1N HCl was prepared according to I.P. 1996. Accurately 8.5 ml of HCl was taken and diluted with freshly prepared distilled water to produce 1000 ml.

Preparation of Stock Solution of Acyclovir in 0.1N HCl:

Weighed accurately about 200 mg of Acyclovir was dissolved in little quantity of 0.1N HCl and volume was adjusted to 100 ml with the same to prepare standard solution having concentration of 1000 µg/ml. From this solution, pipette out 10 ml and made up to 100 ml with 0.1N HCl to produce 100 µg/ml.

Procedure:

From the stock solution, aliquots of 0.4, 0.8, 1.2, 1.6 and 2 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with 0.1N HCl to get 4 to 20 µg/ ml. Absorbance values of these solutions were measured against blank (0.1N HCl) at 255 nm using UV-visible spectrophotometer.

6.1.4.3. Development of Standard Curve of Acyclovir in phosphate buffer p^H 7.4:

Preparation of phosphate buffer p^H 7.4:

Phosphate buffer p^H 7.4 was prepared according to I.P. 1996. Accurately 8.5 ml of phosphate buffer p^H 7.4 was taken and diluted with freshly prepared distilled water to produce 1000 ml.

Preparation of Stock Solution of Acyclovir in phosphate buffer p^H 7.4:

Weighed accurately about 200 mg of Acyclovir was dissolved in little quantity of phosphate buffer p^H 7.4 and volume was adjusted to 100 ml with the same to prepare standard solution having concentration of 1000 µg/ml. From this solution, pipette out 10 ml and made up to 100 ml with phosphate buffer p^H 7.4 to produce 100 µg/ml.

Procedure:

From the stock solution, aliquots of 0.4, 0.8, 1.2, 1.6 and 2 ml were transferred to 10 ml volumetric flasks and final volume was made to 10 ml with phosphate buffer p^H 7.4 to get 4 to 20 µg/ ml. Absorbance values of these solutions were measured against blank phosphate buffer p^H 7.4 at 275 nm using UV-visible spectrophotometer.

B. Compatibility testing of drug with polymer *(IP, 2007; Aulton M.E., 2002; Silverstein R.M, Webster F.X., 2003; Skoog D.A.,et.al.,1996)*

The proper design and formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of all drug substances and excipients to be used in the fabricating the product. Each polymer used in the formulations was blended with the drug levels that are realistic with respect to the final dosage form. Each polymer was thoroughly blended with drug to increase drug - polymer molecular contacts to accelerate the reactions if possible.

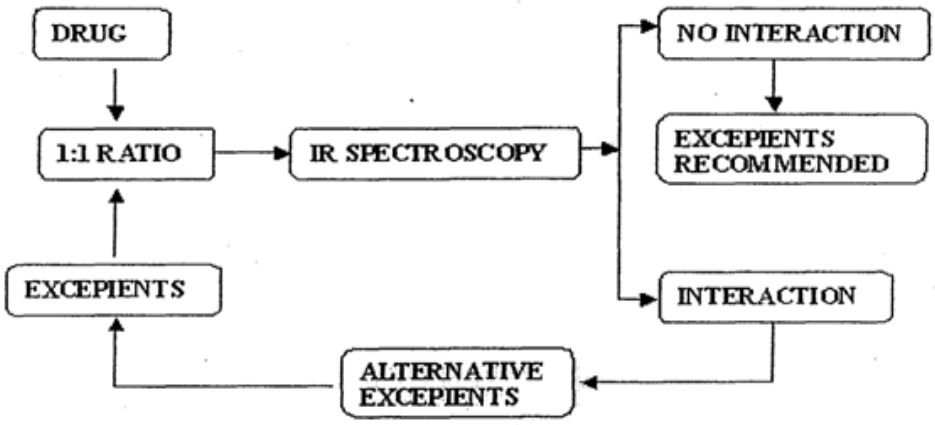


Figure.12: Schematic representation of compatibility studies

A. Fourier Transforms Infra-Red (FTIR) spectroscopy

FTIR study was carried out to check compatibility of drug with polymers. Infrared spectrum of Acyclovir was determined on Fourier transform Infrared Spectrophotometer using KBr dispersion method. The base line correction was done using dried potassium bromide. Then the spectrum of dried mixture of drug and potassium bromide was run followed by drug with various polymers by using Parkin elmer-Pharmaspec-1 FTIR spectrophotometer. The absorption maximums in spectrum obtained with the substance being examined correspond in position and relative intensity to those in the reference spectrum represented in Table 20 and 22, Also Figure 19 to 22 respectively.

B. Preparation and evaluation of Powdered blend *(Lachman L, et al., 1991; Bankar G.S. and Rhodes C.T.,2009; Kabir., et al., 2009; Ghosh S and Barik B., 2009; Umash D., et al., 2009)*

Table 8: Composition of Acyclovir Sustained Release Matrix tablets for formulations

Ingredients (mg/ml/tab)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Acyclovir	200	200	200	200	200	200	200	200	200
Xanthan gum	35	70	105	-	-	-	-	-	-
Sodium Alginate	-	-	-	35	70	105	-	-	-
Chitosan	-	-	-	-	-	-	35	70	105
Starch	79	44	09	79	44	09	79	44	09
Polyvinyl Pyrolidone	20	20	20	20	20	20	20	20	20
Talc	10	10	10	10	10	10	10	10	10
Magnesium Stearate	6	6	6	6	6	6	6	6	6
Total weight	350	350	350	350	350	350	350	350	350

A, Angle of repose

The frictional force in the powder can be measured by the angle of repose.

Angle of repose is calculated by fixed funnel method. In this method, funnel was fixed to a stand so that the lower tip of the funnel was 2.5 cm above the surface; a graph paper was placed o.kn a flat surface. The blend was allowed to fall freely on the graph paper through the funnel, till the tip of the heap formed just touches the funnel. The radius of the heap was noted and from this angle of repose was determined.

Angle of repose θ can be calculated the equation as follows:

$$\text{Tan } \theta = h/r$$

Where, h = height of the heap in cm.

r = radius of the heap in cm.

Table 9: Relationship between Angle of Repose (θ) and Flowability

Angle of Repose (θ)	Flowability
< 20	Excellent
20-30	Good
30-34	Acceptable
> 40	Very poor

a, Bulk Density

For the determination of bulk density a sample of about 2g was poured into a 10 ml graduated cylinder. The cylinder was dropped at 2 seconds interval into a hard wooden surface three times from a height of 2.5 cm.

The volume was recorded and the bulk density was calculated using the formula.

Bulk density = weight of blend /bulk volume of blend

The results are summarized in the table no.24.

b, Tapped Density

A sample of about 2g was poured gently into a 10 ml graduated cylinder. The cylinder was dropped at 2 seconds interval from a height of 2.5cm. The tapped density was calculated by measuring final volume after 100 taps on a wooden surface.

Tap density = weight of blends/ tapped volume of blends

c, Compressibility Index

The packing ability of the granules was evaluated from the change in volume, which is due to rearrangement and packing occurring during tapping. It is expressed as Carr's Compressibility Index (CC %) and is calculated as follows.

$$CI = \frac{(TD - BD)}{TD} x100$$

Where, TD – Tap density

BD – Bulk density

Table 10: Relationship between CC% and Flowability

CC %	Flowability
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
< 40	Very very poor

a. Hausner's Ratio

Hausner's ratio was determined by following equation,

Hausner's Ratio = Tapped bulk density/Loose bulk density

A hausner ratio less than 1.25 indicates good flow while greater than 1.5 indicates poor flow.

6.2. Formulation of Sustained release matrix tablet of Acyclovir

(Lachman L., et al., 1991; Bankar G.S., and Rhodes C.T., 2009; Yadav I.K., et al., 2010)

The tablet was prepared by simple blending of active ingredient with polymers, filler, binder, lubricant and flow promoter followed by direct compression method (Table 5). 50 tablets were prepared for each proposed formulation. Properly weighed Xanthan gum, Sodium Alginate and Chitosan, magnesium stearate, and the active ingredient were then taken in a photo film container and blended in 16 stations Cadmach tablet compression machine and compressed with 10mm flat faced punches by using direct compression technique. Compression force was kept constant for all formulations. The main steps in direct compression methods are,

1. **Sieving**
   - Acyclovir was passed through sieve # 40.
   - Polymers, magnesium stearate were passed through sieve #40.
   - Xanthan gum, Sodium Alginate and Chitosan, polymers are taken with drug in the different ratios
2. **Dry mixing**
   - The above sieved materials were mixed thoroughly by tumbling method in a polythene bag.
3. **Lubrication**
   - The powders were lubricated with Magnesium stearate.
4. **Compression**
   - The lubricated powders were compressed using beveled flat faced punches of 10mm diameter.
   - Parameters like average weight, hardness, and friability are checked during compression as in process quality measures.

The main steps in direct compression methods were

Blending of drug and polymers
↓
Passing through sieve
↓
Lubrication of blend
↓
Compression of lubricated powders

6.3. Evaluation of Sustained release matrix tablet of Acyclovir *(IP, 2007; Lachman L, et al., 1991; Bankar G.S. and Rhodes C.T., 2009)*

a) Thickness

The thickness of the tablets was determined using a vernier caliper. Five tablets from each formulation were evaluated and average values were calculated.

b) Weight variation test *(IP, 2007)*

For weight variation, 20 tablets of each type of formulation were weighed individually on an electronic balance, average weight was calculated and individual tablet weight was then compared with the average value to find out the deviation in weight.

Table 11: Specifications of %Weight variation allowed in tablets as per IP.

Sr. No	Average Weight of tablet	% Deviation
1.	80 mg or less	10
2	More than 80 but less than 250 mg	7.5
3	250 mg or more	5

c) Hardness For each type of formulation, the hardness value of 6 tablets was determined using Monsanto hardness tester.

d) Friability

Friability of Acyclovir tablets was tested using a friabilator (Friability testing apparatus, Electro lab, Mumbai.) A loss of less than 1% in weight was acceptable. The weight of 10 tablets was noted initially (W1) and placed in the friabilator for 4 min /100 rpm. The tablets were reweighed and noted as (W2). The difference in the weight is noted and expressed as percentage.

The percent friability was determined using the formula:

$$\text{Percentage friability} = \frac{W1 - W2}{W1} \text{ X } 100$$

Where, W1=Tablets was noted initially

W2= tablets were reweighed and noted as

Limits for Friability are usually less than 1%.

e) Content uniformity *(IP., 2007)*

Content uniformity was determined by accurately weighing 5 tablets and crushing them in mortar with the help of a pestle. Then an accurately weighed quantity of powder equivalent to 50 mg of drug was transferred to a 50 ml volumetric flask. 50 ml of Methanol was added and shaken. Volume was made upto 50 ml with Methanol. The solution was filtered through whatman filter paper. First few ml of the filtrate was discarded. 1 ml of the filtrate was diluted to 25 ml with Methanol. Then 3 ml of the resulting solution was again diluted to 10 ml with Methanol. The absorbance of the resulting 10 µg/ml solution was recorded at 275nm.

Content uniformity was calculated using formula

$$\% \text{ Purity} = 10 \text{ C } (Au / As)$$

Where, C = concentration, Au and as are absorbance obtained from standard preparation and assay preparations respectively.

f) *In-vitro* dissolution studies *(IP., 2007; Dressman J and Krammer J., 2005; Soni T., et al., 2008; Yeole P.G., et al., 2006)*

The *in vitro* dissolution studies were performed using USP-22 type I dissolution apparatus at 50rpm. Dissolution test was carried out upto 11 hours using 0.1N HCl (P^H 1.2)

solution (900 ml) as dissolution medium at 37 ± 0.5°c for first 2 hours, and P^H 7.4 phosphate buffer solution (900 ml) for the rest of the period. An aliquot (5ml) was withdrawn at specific time intervals and drug content was determined by U.V. spectrophotometer (Schimadzu, 1601) at 255.55 nm for P^H 1.2 and 275 nm in P^H 7.4. It was made clear that none of the ingredients used in the matrix formulations interfered with the assay. The release studies were conducted in triplicate.

g) Data Analysis (Curve Fitting Analysis) *(Brahmankar D.M and Jaiswal S.B., 2005; Chandira., et al., 2009)*

To analyze the mechanism of the drug release rate kinetics of the dosage form, the data obtained were graphed as:

i. Cumulative percentage drug released Vs Time (*In-vitro* drug release plots)

ii. Cumulative percentage drug released Vs Square root of time (Higuchi's plots)

iii. Log cumulative percentage drug remaining Vs Time (First order plots)

iv. Log percentage drug released Vs Log time (Peppas plots)

Higuchi release model

To study the Higuchi release kinetics, the release rate data was fitted to the following equation. $F = K.t^{1/2}$

Where, 'F' is the amount of drug release,

'K' is the release rate constant, and 't' is the release time.

When the data is plotted as accumulative drug released versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

Korsmeyer and Peppas release model

The release rate data were fitted to the following equation,

$$Mt / M\infty = K. t^n$$

Where, $Mt / M\infty$ is the fraction of drug release,

'K' is the release constant,

't' is the release time,

'n' is the diffusional exponent for the drug release that dependent on the shape of the matrix dosage form.

When the data is plotted as Log of released versus Log time, yields as straight line with a slope equal to 'n' and the 'K' can be obtained from Y – intercept.

For non- Fickian release the 'n' values falls between 0.5 and 1.0 while for Fickian (case I) diffusion n= 0.5 and zero order release (case II transport) n= 1.0.

Zero order release rate kinetics

To study the zero-order release kinetics the release rate date are fitted to the following equation.

$$F = Kt$$

Where 'F' is the fraction of drug release,

'K' is the release rate constant and

't' is the release time.

When the data is plotted as cumulative percent drug release versus time, if the plot is linear then the date obeys zero-order release kinetics, with a slope equal to K.

6.4. Stability studies *(Manavalan R., 2004; Yadav I.K., et al., 2010)*

Tablets were placed in tightly screwed bottles. The bottles were then kept in a stability chamber, which was maintained at 40^0 c and 75% RH.

The samples were withdrawn after 30 days and all the tests like hardness, friability, content uniformity and *in vitro* dissolution were carried out.

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "Stability testing of New Drug Substances and Products describes the stability test requirements for drug registration application in the European Union, Japan and the States of America.

ICH specifies the length of study and storage conditions;

Long-Term Testing: 25^0 C ± 2^0 C at 60% RH ± 5% for 12 Months

Accelerated Testing: 40^0 C ± 2^0 C at 75% RH ± 5% for 6 Months

Method:

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 25^0 C at 60% and 40^0 C at 75 % RH for 3 months and evaluated for their physical appearance, drug content and drug excipients compatibility at specified intervals of times.

RESULTS AND DISCUSSION

7. RESULTS AND DISCUSSION

7.1. Preformulation parameters:

7.1.1. Organoleptic Properties (*Lachman L., 1991*)

Physical state : Fine powder

Colour : A white fine powder

Odour : Characteristic

Taste : Bitter to alkaline

7.1.2. Melting Point: *(IP., 2007)*

Melting point of Acyclovir was found to be 256.6 $\pm 1.15^0$C with decomposition. The official melting point range for Acyclovir is between 256-258°C. Hence, results were complied the limits specified in official Book.

7.1.3. Solubility Profile:

Table 12: Solubility of Acyclovir in various solvents

Name of solvent	Solubility
Dilute HCl	Soluble
Water	Slightly soluble
Alcohol	Sparingly soluble
Acetone	Insoluble

The results were complied with official solubility of Acyclovir (IP 2007)

7.1.4. UV Spectroscopy (λ max):

7.1.4.1. Determination of λ max for Acyclovir by using Distilled Water:

The absorption maximum for Acyclovir in Distilled Water was found to be 252 nm and it is shown in Figure 13.

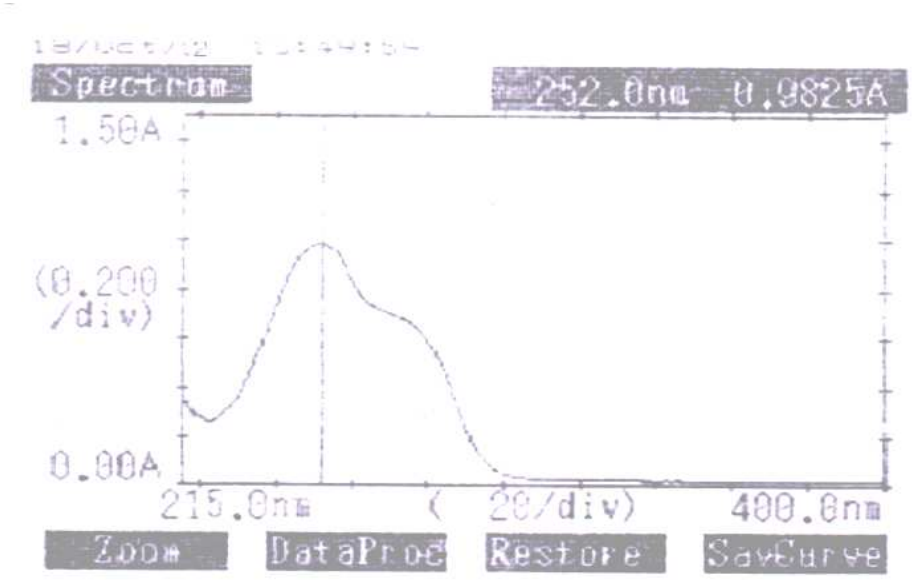


Figure. 13: λ max Observed for Acyclovir in Distilled Water

7.1.4.2. Preparation of Standard Curve for Acyclovir by using Distilled Water:

UV absorption spectrum of Acyclovir in Distilled Water showed λ max at 252 nm. Absorbance obtained for various concentrations of Acyclovir in distilled water was given in Table 13. The graph of absorbance Vs. concentration for Acyclovir was found to be linear in the concentration range of 4 - 20 µg/ml. The drug obeys Beer - Lambert's law in the range of 4 - 20 µg/ml which was shown in Figure 14. The calibration parameters were shown in Table 14.

Table 13: Data of concentration Vs absorbance for Acyclovir in Distilled Water

S. No.	Concentration (µg/ml)	Absorbance at 252nm
1.	0	0
2.	4	0.191
3.	8	0.375
4.	12	0.563
5.	16	0.744
6.	20	0.931

Table 14: Data of calibration curve parameter in Distilled Water

S. No.	Parameters	Values
1.	Correlation Coefficient (r)	0.9999
2.	Slope (m)	0.04644
3.	Intercept (c)	0.00290

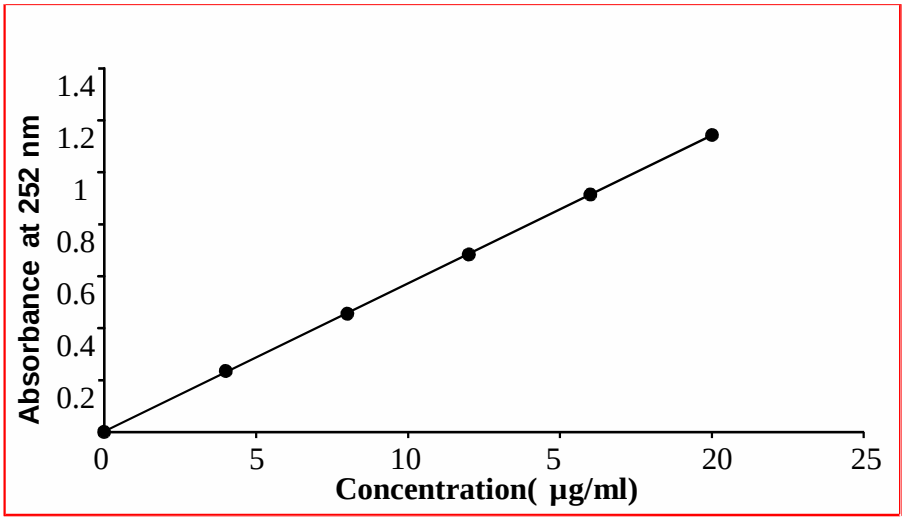


Figure 14: Standard graph for Acyclovir in Distilled Water

7.1.4.3. Determination of λ_{max} for Acyclovir by using 0.1N HCl:

The absorption maximum for Acyclovir by using 0.1N HCl was found to be 255.55 nm and it is shown in Figure 15.

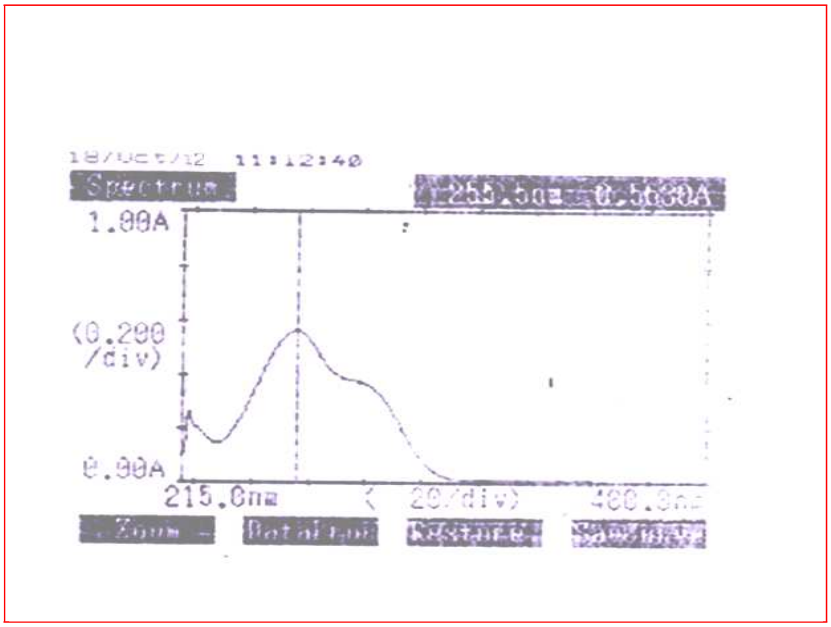


Fig. 15: λ_{max} Observed for Acyclovir in 0.1N HCl

7.1.4.4. Preparation of Standard Curve for Acyclovir by using 0.1N HCl:

The UV absorption spectrum of Acyclovir in 0.1N HCl shown λ_{max} at 255.5nm. Absorbance obtained for various concentrations of Acyclovir in 0.1N HCl were given in Table 15. The graph of absorbance Vs. concentration for Acyclovir was found to be linear in the concentration range of 4 - 20µg /ml. The drug obeys Beer - Lambert's law in the range of 4 - 20µg /ml which was shown in Figure 16. The calibration parameters were shown in Table 16.

Table 15: Data of concentration Vs absorbance for Acyclovir in 0.1N HCl

S. No.	Concentration (µg/ml)	Absorbance at 255.5 nm
1.	0	0.000
2.	4	0.235
3.	8	0.455
4.	12	0.683
5.	16	0.914
6.	20	1.143

Table 16: Data for calibration curve parameters in 0.1N HCl

S. No.	Parameters	Values
1.	Correlation Coefficient (r)	0.9999
2.	Slope (m)	0.057
3.	Intercept (c)	0.0016

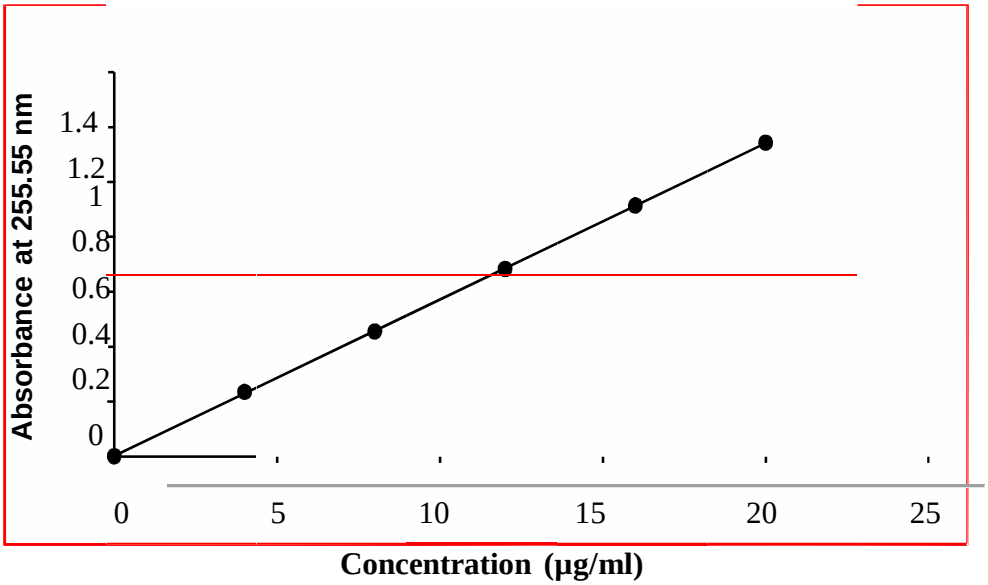


Fig. 16: Standard graph of Acyclovir in 0.1N HCl

7.1.4.5. Determination of λ_{max} for Acyclovir by using Phosphate buffer P^H 7.4:

The absorption maximum for Acyclovir was found to be 275 nm and it is shown in Figure 17.

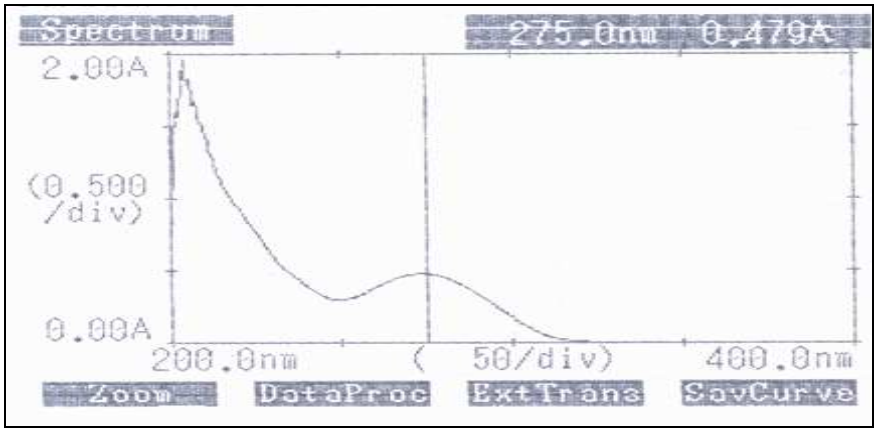


Figure.17 λ_{max} observed for Acyclovir in Phosphate buffer P^H 7.4

7.1.4.6. Preparation of Standard Curve for Acyclovir By using in Phosphate buffer P^H 7.4:

UV absorption spectrum of Acyclovir in Phosphate buffer P^H 7.4 showed λ max at 275 nm. Absorbance obtained from various concentrations of Acyclovir Phosphate buffer P^H 7.4 were given in table 17. The graph of absorbance V*s* concentration for Acyclovir was found to be linear in the concentration range of 4 – 20 μg/ml. The drug obeys Beer-Lambert's law in the range of 5 – 30 μg /ml.

Table 17: Data of Concentration Vs absorbance for Acyclovir in Phosphate buffer P^H 7.4

Sr. No.	Concentration (μg/ml)	Absorbance(nm)
1	0	0.0000
2	4	0.110
3	8	0.209
4	12	0.327
5	16	0.414
6	20	0.484

Table 18: Data of Calibration Curve Parameter in Phosphate buffer P^H 7.4

Sr. No.	Parameters	Values
1	Correlation coefficient (r)	0.9991
2	Slope (m)	40.10
3	Intercept(c)	0.206

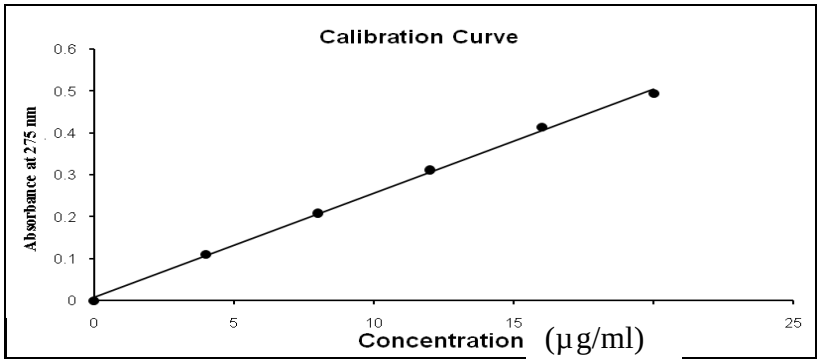


Figure 18: Standard graph of Acyclovir in Phosphate buffer P^H 7.4

7.1.5. Quantification of Drug:

The percentage purity of drug was calculated by using calibration graph method (least square method) and the data has been shown in Table 19.

Table 19: Percentage purity of pure drug Acyclovir

S. No.	Percentage Purity (%)	Average Percentage Purity* (%)
1.	101.35	101.03 ± 0.40
2.	100.67	
3.	101.20	

*All the values are expressed as mean ± SD, n = 3

The percentage purity for Acyclovir in IP 2007 is not less than 98.0 % and not more than 102.0 % of the stated amount of Acyclovir. The percentage purity of Acyclovir was found to be 101.03 ± 0.40. So, it stands within the limits of IP 2007.

7.1.6. Loss on Drying:

The percentage loss on drying after 3 hours was found to be as follows

Table 20: Percentage loss on drying for Acyclovir

S. No	Percentage LOD	*Avg. percentage LOD
1	0.320	0.407±0.070
2	0.451	
3	0.483	

*All values are expressed as mean± S.D., n=3

The sample passes test for loss on drying as per the limit specified in IP, 2007 (N.M.T.-1)

7.1.7: Identification and Drug polymer interaction Study

a) FTIR Spectroscopy:

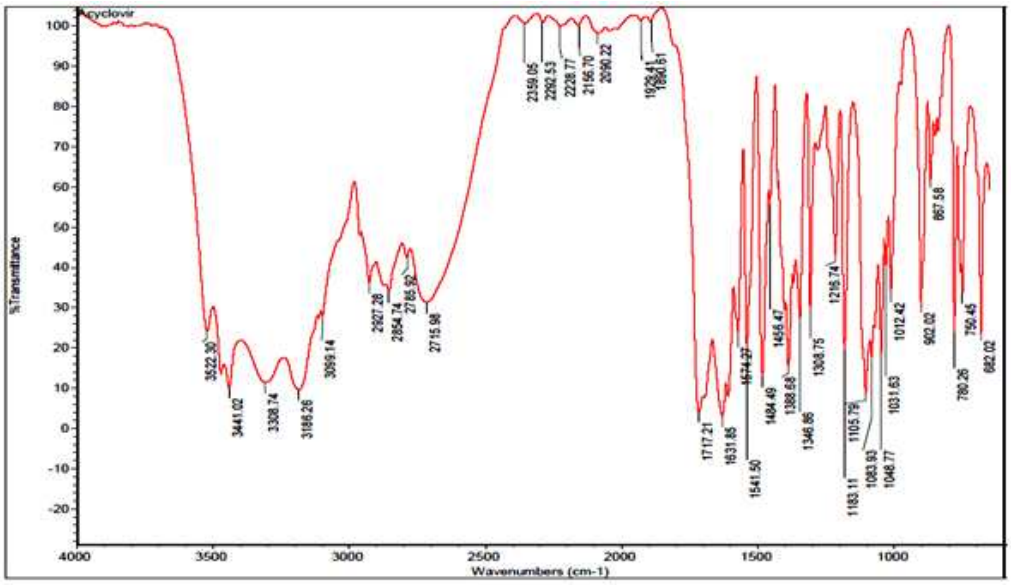


Figure 19: FTIR Spectrum of pure drug Acyclovir

Table 21: Characteristic frequencies in FTIR spectrum of Acyclovir

S.No.	Wave number (cm^{-1})	Inference
1	3441.02	N-H stretching
2	3308.74	O-H stretching
3	3099.14	C-H stretching
4	1717.21	C=O stretching
5	1541.50	C=C and C=N stretching
6	1308.75	$-CH_2$ Wagging and twisting
7	1216.74	Aryl alkyl ether
8	1105.79	C-O stretching
9	1083.93	C-O-C stretching

The drug was confirmed as Acyclovir with results obtained from FTIR spectrum analysis.

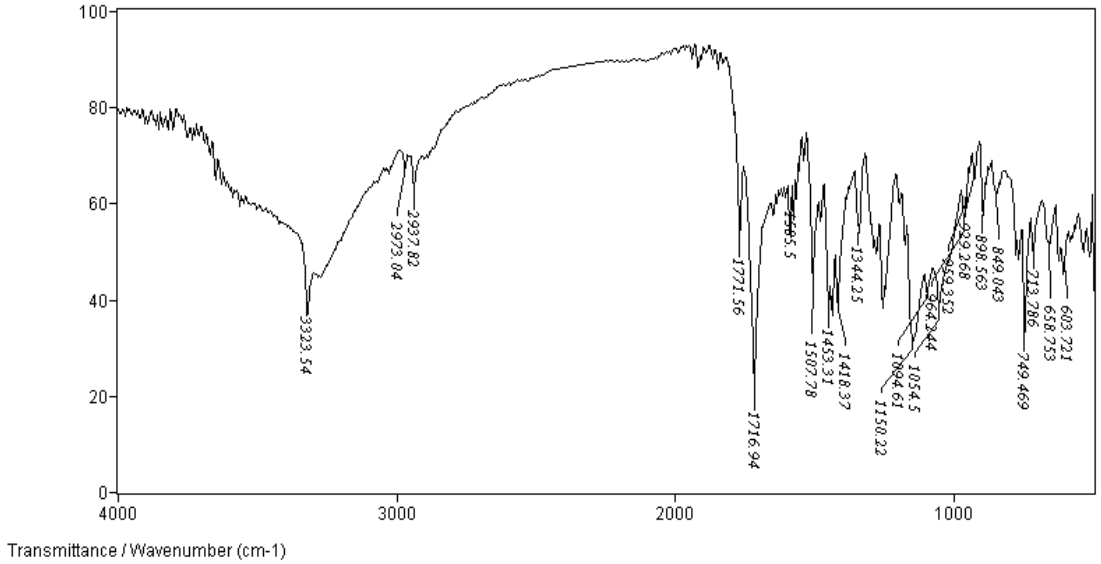


Figure 20: FTIR Spectrum of Acyclovir with Xanthan Gum

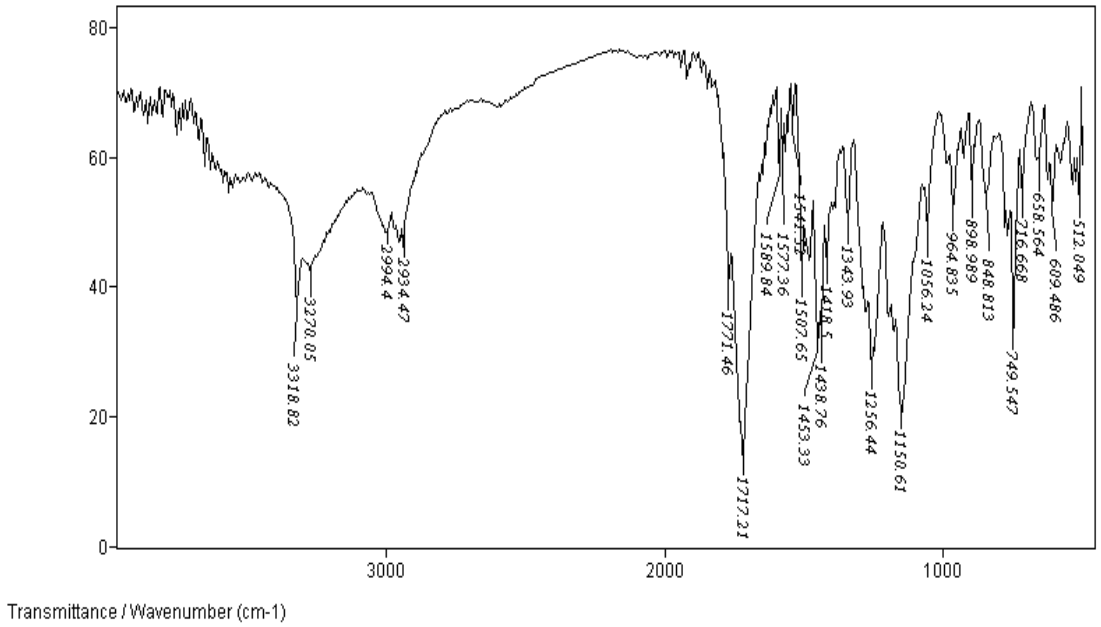


Figure 21: FTIR Spectrum of Acyclovir with Sodium Alginate

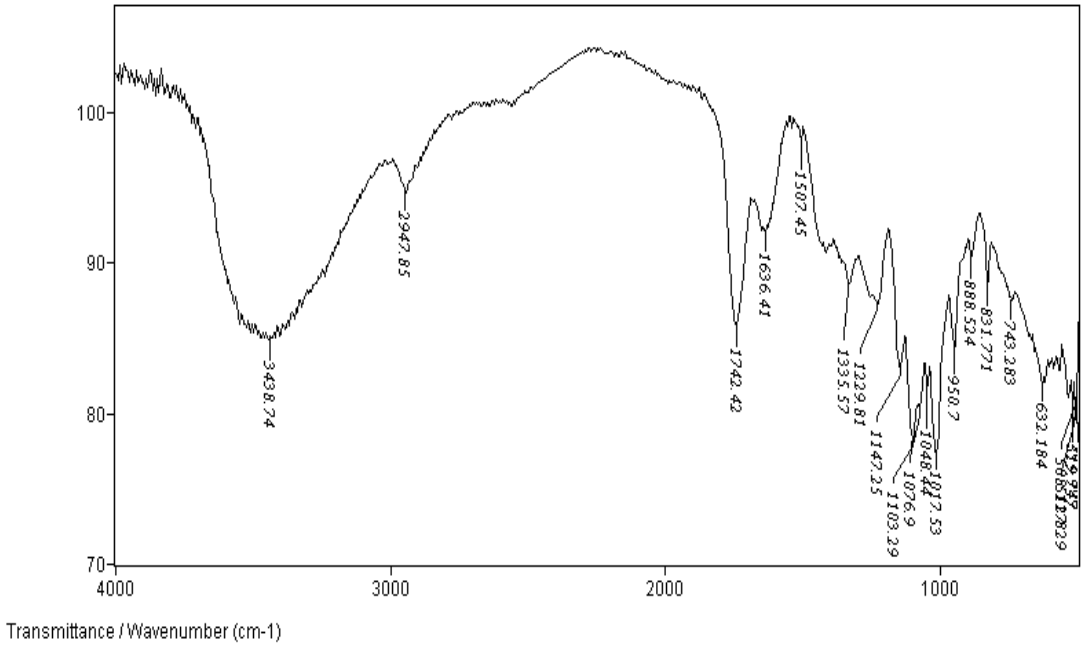


Figure 22: FTIR Spectrum of Acyclovir with Chitosan

FTIR spectroscopy was used to ensure that no chemical interaction between the drugs and polymers had occurred. From the FTIR spectral Figures 19 to 22 interpretations the

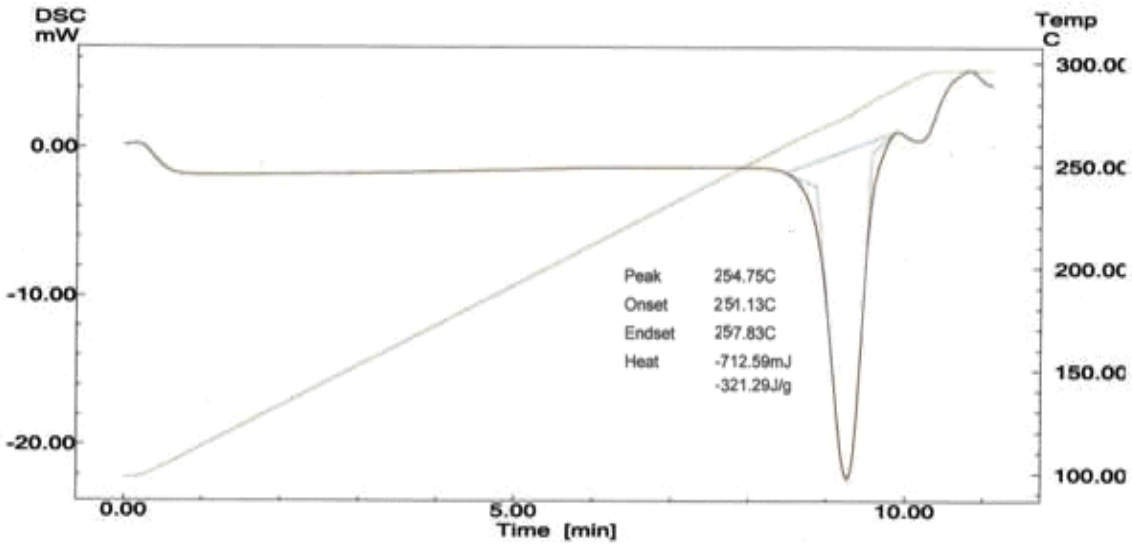
following result was obtained. The FTIR of Acyclovir and combination of polymers shows intense band in the Table 22 as follows.

Sr. No	Name of the ingredient	-C = O	-COOH	-NH	-OH
1.	Acyclovir	1717.21	1771.95	3441.02	3308.74
2.	Acyclovir and Xanthan Gum	1716.94	1771.56	3323.54	2979.04
3.	Acyclovir and Sodium Alginate	1717.21	1771.46	3318.82	3270.05
3.	Acyclovir and Chitosan	1636.41	1742.42	3438.74	2947.85

Table 22: FTIR peaks of functional groups (cm^{-1})

b) Differential Scanning Calorimetry (DSC)

The compatibility and interactions between drugs and polymer were checked using DSC, results obtained were shown in Figure 23 to 26



.**Figure 23:** DSC Curve of pure Acyclovir

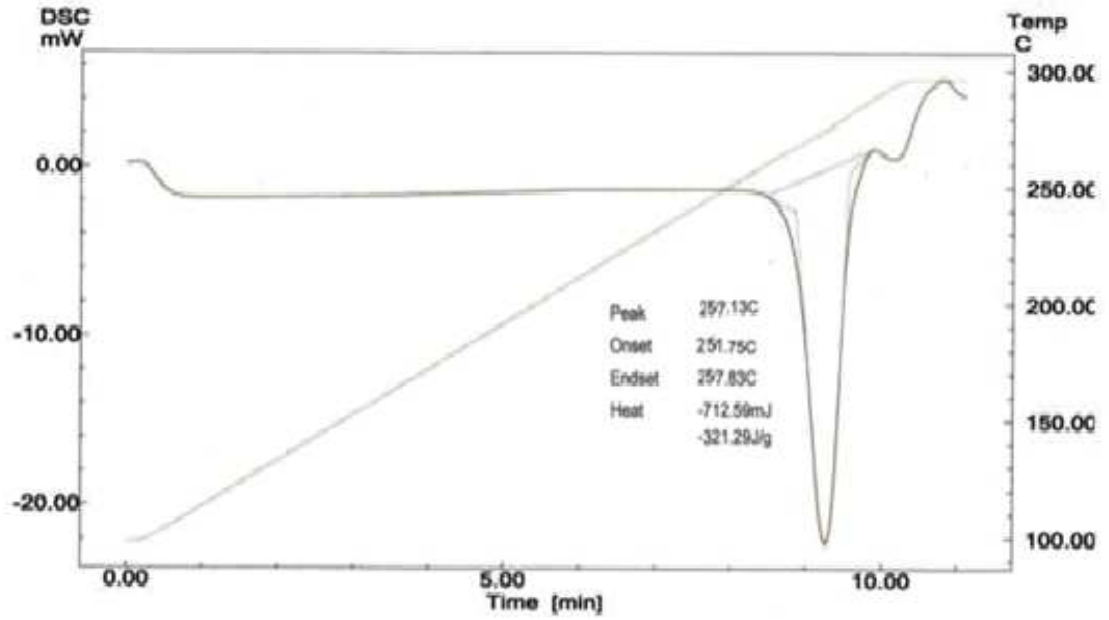


Figure 24: DSC Curve of Acyclovir with Xanthann Gum

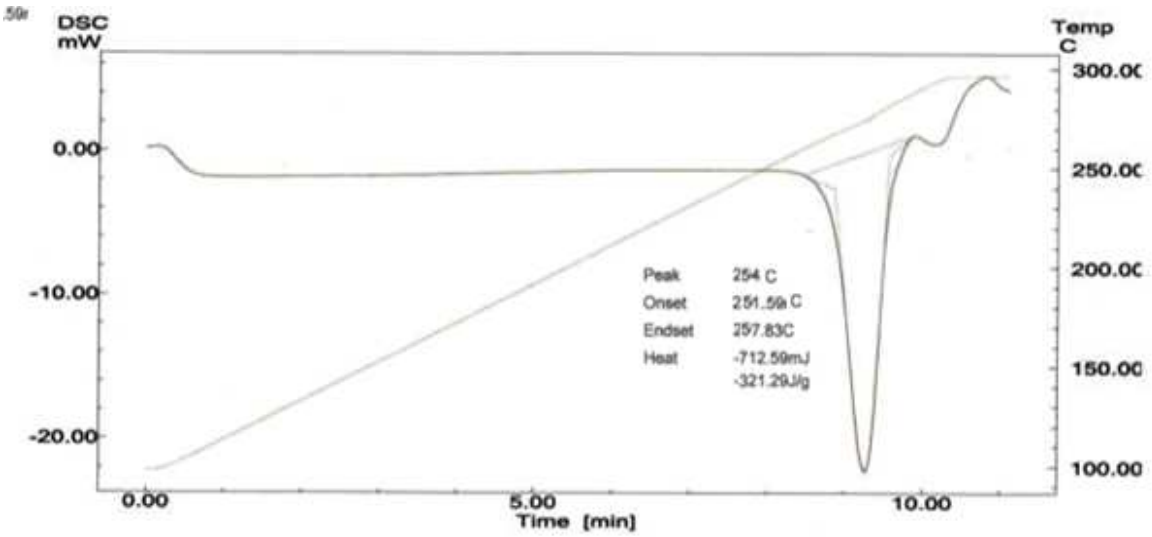


Figure 25 DSC Curve of Acyclovir with Sodium Alginate

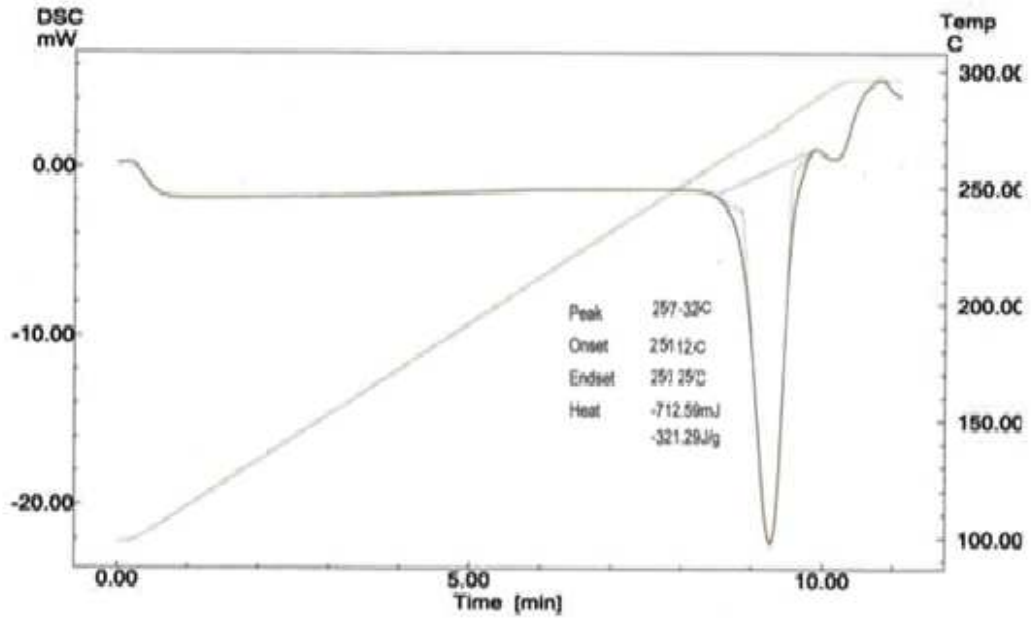


Figure 26: DSC Curve of Acyclovir with Chitosan

Table 23: Data of DSC Thermogram Parameters

Sr. No	Name of ingredients and physical mixtures used in formulation	Temperature at which peak obtained
1.	Acyclovir	254.75^0C
2.	Acyclovir with Xanthan gum	257.13^0C
3.	Acyclovir with Sodium Alginate	254.00^0C
4.	Acyclovir with Chitosan	257.32^0C

DSC thermogram showed that there was no any major difference in onset temperature and peak temperature, Which was compared with pure drug Acyclovir thermogram shown in Figure 23. The data of thermogram parameters were shown in Table 23.

A. Physical Characterization of powder blend

The powder blends were prepared by mixing of various ingredients mentioned in table no.8 and used for characterization of various flow properties of powder.

Table 24: Flow properties of powder blend for formulations F1 to F9

Formulation Code	Angle of repose (θ)*	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Hausner ratio (HR)*	Carr's index (IC)*
F1	21.50±0.31	0.590±0.007	0.879±0.078	1.14±0.033	12.41±0.56
F2	20.98±0.23	0.683±0.001	0.781±0.010	1.12±0.03	11.88±2.09
F3	20.35±0.59	0.650±0.009	0.778±0.009	1.13±0.010	10.89±1.50
F4	22.38±0.21	0.675±0.07	0.769±0.004	1.13±0.012	10.87±0.84
F5	22.81±0.44	0.687±0.006	0.789±0.07	1.15±0.002	11.93±0.68
F6	21.07±0.92	0.629±0.008	0.767±0.013	1.12±0.07	12.33±1.35
F7	20.01±0.61	0.680±0.001	0.763±0.05	1.14±0.04	11.87±1.05
F8	20.48±0.70	0.627±0.007	0.890±0.07	1.11±0.012	12.78±1.84
F9	21.45±1.21	0.693±0.005	0.798±0.03	1.14±0.04	13.40±1.81

*All the values are expressed as mean± SD, n=3.

a) Bulk Density (BD)

The powder blends of formulations have the bulk density ranged between 0.590±0.007 to 0.693±0.0005 (gm/cm3).

b) Tapped bulk density (TBD)

The powder blends of formulations have the tapped bulk density ranged between 0.763±0.05 to 0.890±0.07 (gm/cm3). These values indicate good packing characteristics and the powder was not bulky.

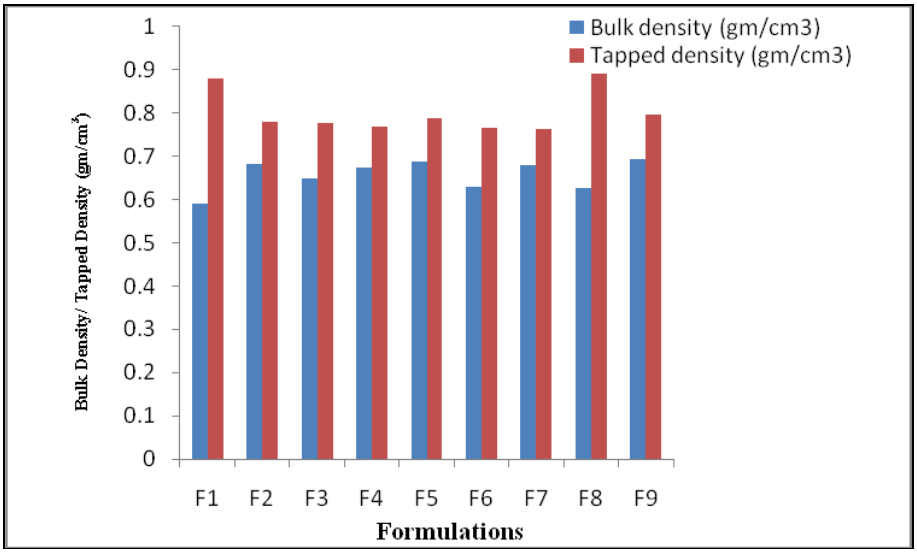


Figure 27: Comparison of Physical Characteristics of Bulk density and Tapped density for Formulations F1 to F9

c) Carr's Compressibility Index

The Carr's index for all the formulations was found to be below 13.40% indicating that the powders have a excellent compressibility.

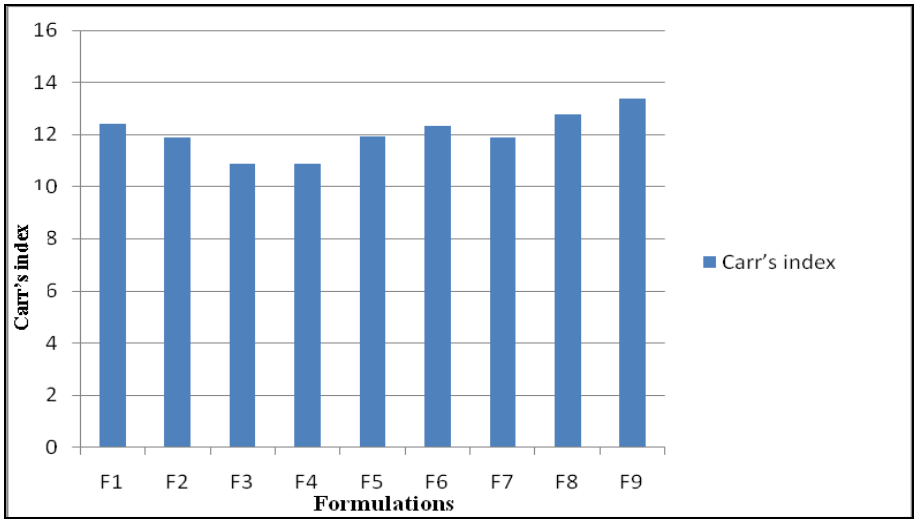


Figure 28: Comparison of Physical Characteristics of Carr´s index for Formulations F1 to F9

d) Hausner's Ratio

The hausner's ratio for all the formulations was found to be <1.15, indicating good flow properties.

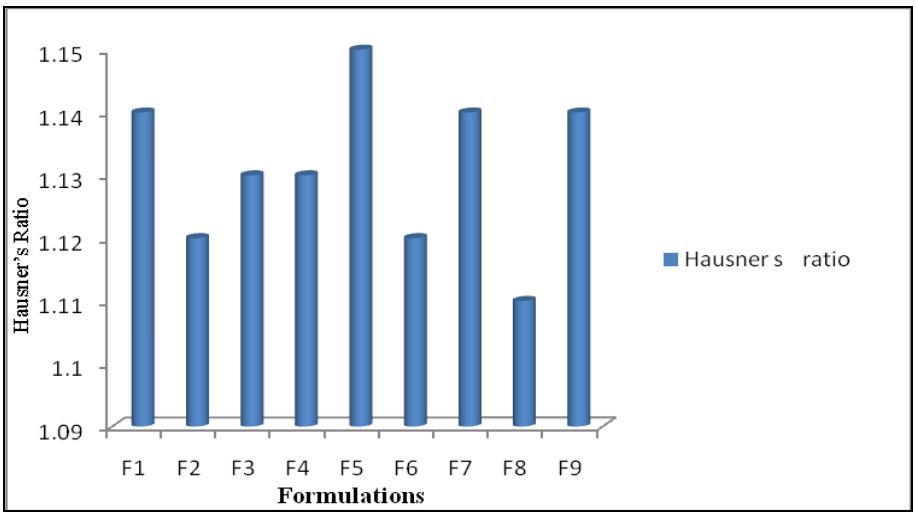


Figure 29: Comparison of Physical Characteristics of Hausner's ratio for Formulations F1 to F9

e) Angle of repose

The flow properties of powder were analyzed by determining angle of repose which was found to be between 20.01±0.61 to 22.81±0.44 indicating excellent flow property.

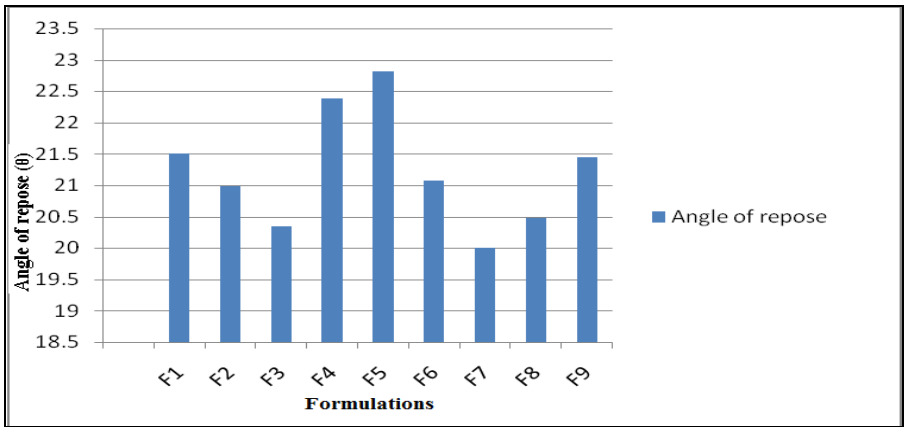


Figure 30: Comparison of Physical Characteristics of Angle of repose for Formulations F1 to F9

7.2. EVALUATION OF SUSTANIED RELEASE MATRIX TABLET

a) Appearance

The tablets were observed visually and did not show any defect such as capping, chipping and lamination.

b) Physical characteristic

The physical characteristic of Acyclovir sustained release matrix tablets (F1 to F9) such as thickness, diameter, hardness, friability, weight variation and drug content were determined and results of the formulations (F1 to F9) found to be within the limits specified in official books.

Table 25: Physico-Chemical Characterization for Formulations F1 to F 9

Code	Thickness (mm)*	Weight variation test (%)	Hardness (kg/cm^2)*	Friability (%)*	Drug content (%)*
F1	3.53±0.24	345±2.30	5.77±0.50	0.43±0.07	97.56±6.64
F2	3.48±0.027	332±2.04	5.60±0.64	0.47±0.05	100.95±6.90
F3	3.24±0.065	351±1.90	5.58±0.37	0.49±0.08	96.32±5.92
F4	3.84±0.064	352±2.20	5.57±0.14	0.46±0.03	97.20±5.79
F5	3.44±0.039	351±2.12	5.66±0.54	0.47±0.05	101.11±2.65
F6	3.54±0.051	353±1.92	5.86±0.40	0.54±0.04	97.99±5.18
F7	3.52±0.039	352±2.09	5.83±0.25	0.53±0.09	99.14±5.37
F8	3.57±0.053	352±2.12	5.96±0.48	0.49±0.04	99.15±4.68
F9	3.51±0.046	350±2.03	5.78±0.37	0.46±0.05	100.11±2.38

*All the values are expressed as mean± SD, n=3

c) Dimension (Thickness and Diameter)

Thickness and diameter specifications may be set on an individual product basis. Excessive variation in the tablet thickness and diameter can result in problems with packaging as well as consumer acceptance. There were no marked variations in the thickness and diameter of tablets within each formulation indicating uniform behavior of granules throughout the compression process.

The sizes (diameter) of the tablets of all formulations were found to be 10.00±0.0 mm.

d) Tablet Hardness

A difference in tablet hardness reflects difference in tablet density and porosity. In which turn are supposed to result in different release pattern of the drug by affecting the rate of penetration of dissolution fluid at the surface of the tablet and formation of gel barrier. The hardness of tablets was found to be in the range of 5.57±0.14 kg/cm^2 to 5.96±0.48kg/cm^2. This indicates good tablet strength

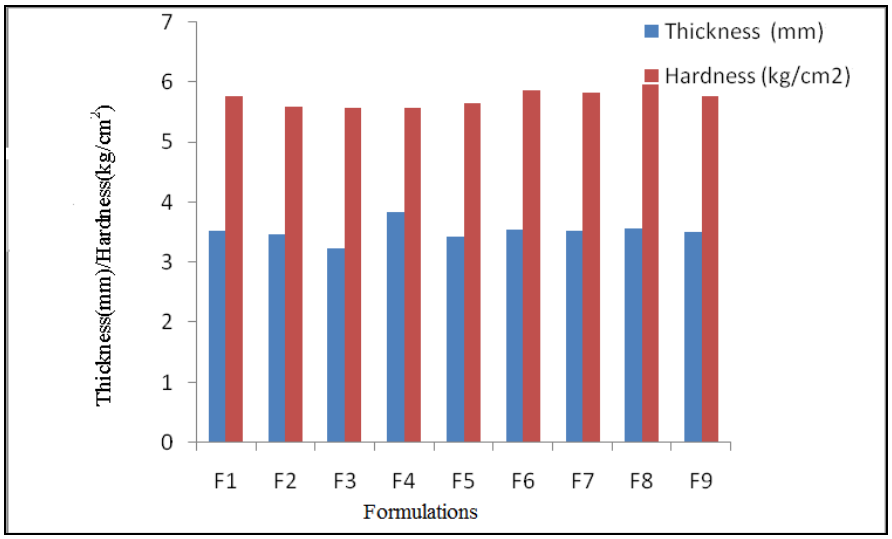


Figure 31: Comparison Study of Tablets Thickness & Hardness for Formulations F1 to F9

e) Percent Friability

Percentage friability of all the formulations was found between 0.43±0.07 to 0.54±0.04%. This indicated good handling property of the prepared Sustained Release tablet.

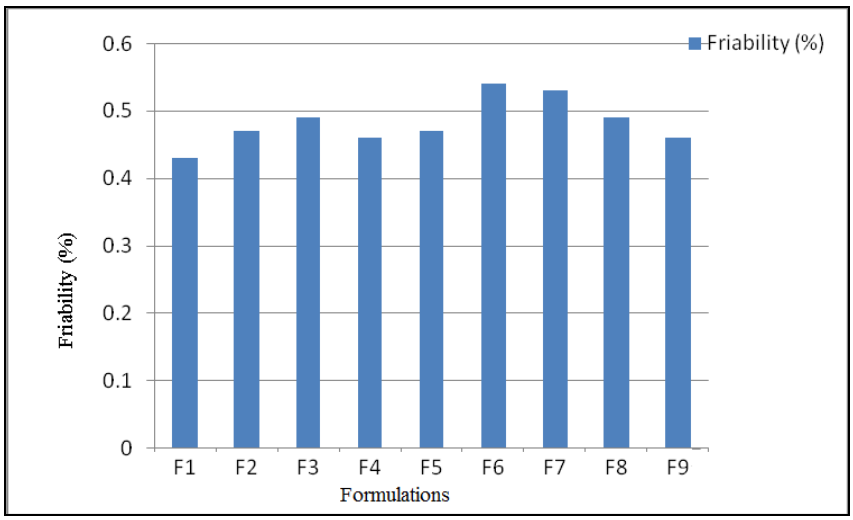


Figure 32: Comparison Study of Tablets friability for Formulations F1to F9

f) Weight Variation

A tablet is designed to contain a specific amount of drug. When the average mass of the tablet is 350 mg the pharmacopeial limit for percentage deviation is ± 5 %. The percentage deviation from average tablet weight for all the tablet was found to be within the specified limits and hence all formulations complied with the test for weight variation according to the pharmacopeial specifications.

g) Drug content of Acyclovir

The content of active ingredients in the formulation was found to be between 96.32±5.92 to 101.11±2.65 % w/w, which is within the specified limit as per Indian Pharmacopoeia 1996 (i.e. 90-110% w/w).

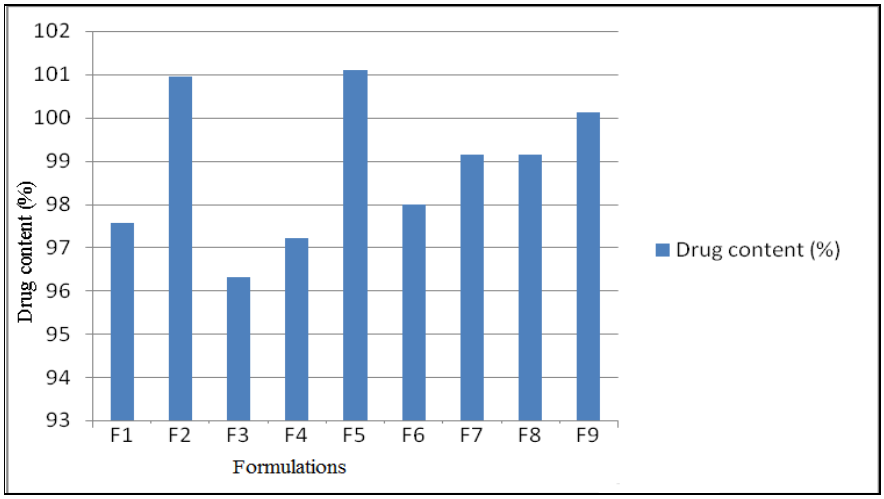


Figure 33: Comparison Study of Tablets of Drug Content for Formulations F1to F9

h) *In-Vitro* Dissolution Studies

Table 26: *In-vitro* drug released profile of formulation F1

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative % drug released
0	0.1 N HCl	0	0
0.5		5.09±0.12	5.09±0.12
1		10.49±1.25	10.49±1.50
1.5		14.22±0.23	14.23±0.25
2		17.63±0.53	17.63±0.55
2.5	Phosphate Buffer pH 7.4	16.78±0.09	34.41±0.09
3		36.55±0.14	54.18±0.14
4		51.33±0.44	68.96±0.44
5		69.33±2.79	86.96±2.79
6		79.78±1.01	97.41±1.01
7		-	-
8		-	-
9		-	-
10		-	-
11		-	-

*All values are expressed as mean ±SD, n=3.

Table 27: *In-vitro* drug released profile of formulation F2

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative % drug released
0	0.1 N HCl	0	0
0.5		3.96±0.38	3.96±0.38
1		7.10±0.46	7.10±0.46
1.5		11.61±0.66	11.61±0.66
2		13.45±0.67	13.45±0.67
2.5		18.97±1.98	32.42±1.98
3		27.82±0.57	41.27±0.57
4		44.64±1.64	58.09±1.64
5		52.82±1.43	66.27±1.43
6		63.67±1.11	77.12±1.11
7		76.53±5.28	89.98±5.28
8		85.42±1.26	98.87±1.26
9		-	-
10		-	-
11		-	-

*****All values are expressed as mean ±SD, n=3.

Table 28: *In-vitro* drug released profile of formulation F3

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative % drug released
0	0.1 N HCl	0	0
0.5		3.78±0.18	2.78±o.18
1		8.13±0.69	8.13±0.69
1.5		13.89±0.56	13.88±0.57
2		17.56±1.08	17.56±1.09
2.5	Phosphate Buffer pH 7.4	15.08±0.40	32.64±0.40
3		27.95±1.08	45.51±1.08
4		33.45±0.27	51.01±0.27
5		56.97±0.95	74.53±0.95
6		61.70±3.38	79.26±3.38
7		75.15±5.61	92.71±5.61
8		80.55±0.95	98.11±0.95
9		-	-
10		-	-
11		-	-

*****All values are expressed as mean ±SD, n=3.

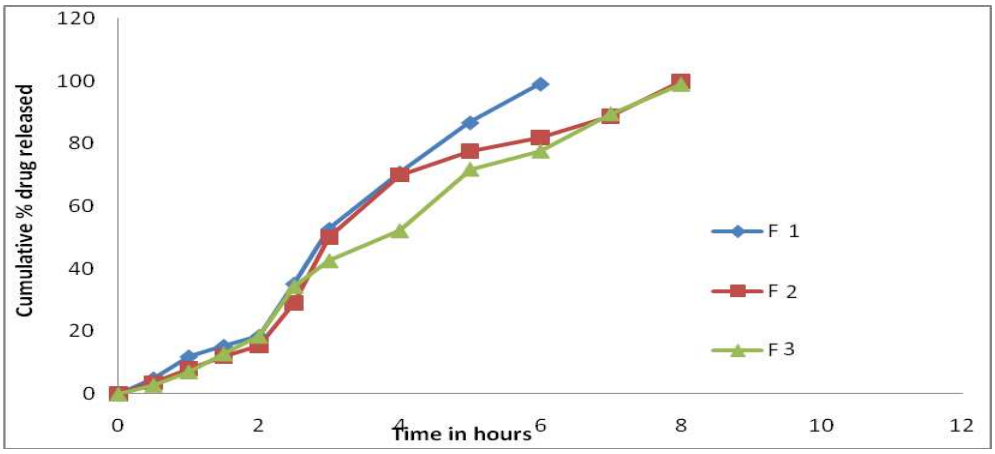


Figure 34: *In-vitro* Drug Released profile curve of formulations F1 to F3

Table 29: *In-vitro* drug released profile of formulation F4

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative% drug released
0	0.1 N HCl	0	0
0.5		4.95±0.72	4.95±0.72
1		10.15±0.96	10.15±0.98
1.5		15.97±0.35	15.97±0.36
2		19.09±0.29	19.07±0.28
2.5	Phosphate Buffer pH 7.4	17.01±0.11	36.1±0.11
3		22.09±0.09	41.18±0.09
4		33.11±0.82	52.2±0.82
5		54.29±0.65	73.38±0.65
6		64.97±0.61	84.06±0.61
7		71.84±0.37	90.93±0.37
8		80.61±0.48	99.70±0.48
9		-	-
10		-	-
11		-	-

*****All values are expressed as mean ±SD, n=3.

Table 30: *In-vitro* drug released profile of formulation F5

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative% drug released
0	0.1 N HCl	0	0
0.5		3.66±0.13	3.66±0.13
1		8.14±0.28	8.14±0.28
1.5		12.14±0.40	12.14±0.40
2		15.45±0.38	15.45±0.38
2.5	Phosphate Buffer pH 7.4	13.80±0.55	29.25±0.55
3		34.53±0.98	49.98±0.99
4		54.45±0.58	69.94±0.61
5		62.13±0.50	77.58±0.22
6		66.50±0.87	81.95±0.88
7		73.25±0.47	88.70±0.53
8		84.29±0.05	99.74±0.05
9		-	-
10		-	-
11		-	-

*****All values are expressed as mean ±SD, n=3.

Table 31: *In-vitro* drug released profile of formulation F6

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative% drug released
0	0.1 N HCl	0	0
0.5		3.96±0.85	3.96±0.85
1		6.19±0.52	6.19±0.52
1.5		7.95±0.24	7.95±0.24
2		12.81±1.19	12.81±1.19
2.5	Phosphate Buffer pH 7.4	6.35±0.25	19.16±0.25
3		14.98±0.54	27.79±0.54
4		26.91±1.58	39.72±1.58
5		40.49±1.52	53.3±1.52
6		51.71±2.32	76.04±2.32
7		63.23±1.55	75.30±1.55
8		71.35±0.82	84.16±0.82
9		77.90±0.44	90.71±0.44
10		86.50±4.74	99.31±4.74
11		-	-

*****All values are expressed as mean ±SD, n=3.

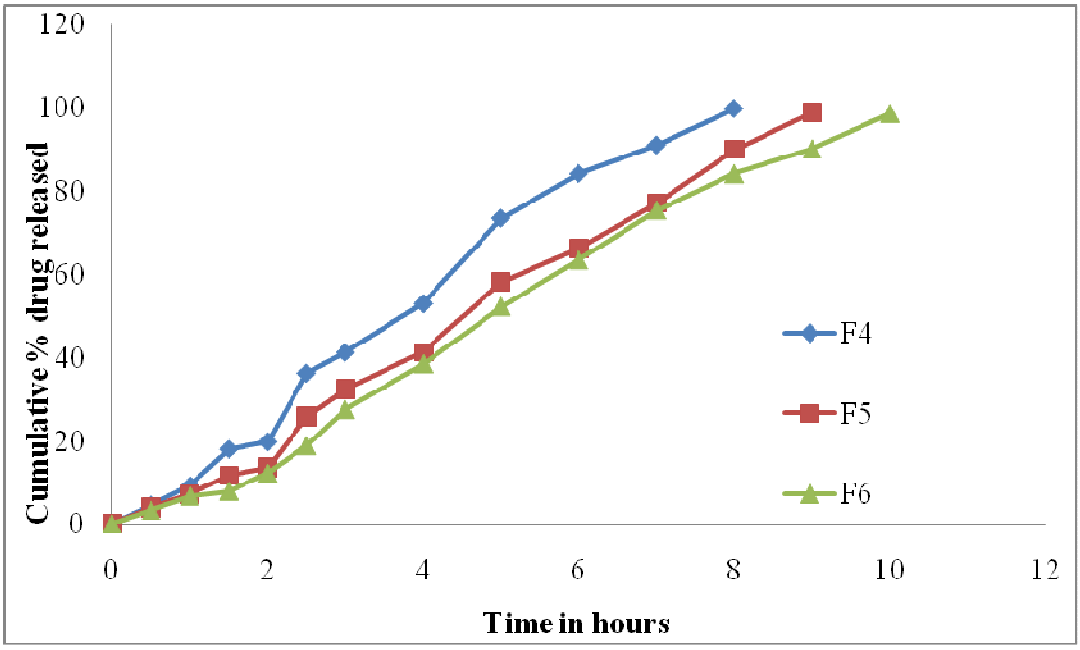


Figure 35: *In-vitro* drug released profile curve of formulations F4 to F6

Table 32: *In-vitro* drug released profile of formulation F7

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative% drug released
0	0.1 N HCl	0	0
0.5		4.10±0.65	4.10±0.65
1		8.70±0.34	8.70±0.34
1.5		13.78±0.22	13.78±0.22
2		17.04±0.24	17.04±0.24
2.5	Phosphate Buffer pH 7.4	13.52±0.87	30.56±0.87
3		27.30±0.91	44.34±0.91
4		41.07±1.20	58.11±1.20
5		47.19±0.73	64.23±0.73
6		56.45±2.29	73.49±2.29
7		65.07±2.09	82.11±2.09
8		76.27±0.98	93.31±0.98
9		80.31±0.87	97.35±0.87
10		-	-

*****All values are expressed as mean ±SD, n=3.

Table 33: *In-vitro* drug released profile of formulation F8

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative% drug released
0	0.1 N HCl	0	0
0.5		3.44±0.29	3.44±0.29
1		6.77±0.41	6.77±0.41
1.5		10.73±0.47	10.73±0.47
2		12.19±0.40	12.19±0.40
2.5	Phosphate Buffer pH 7.4	8.63±0.39	20.82±0.39
3		24.81±1.77	37.00±1.77
4		33.43±1.12	45.62±1.12
5		44.92±1.62	57.11±1.62
6		56.95±1.04	69.14±1.04
7		65.42±1.34	77.61±1.34
8		75.72±0.45	87.91±0.52
9		82.06±1.32	94.25±1.32
10		86.31±0.91	98.50±0.91
11		-	-

*****All values are expressed as mean ±SD, n=3.

Table 34: *In-vitro* drug released profile of formulation F9

Time (hours)	Dissolution Medium	% Drug Released*	Cumulative% drug released
0	0.1 N HCl	0	0
0.5		2.93±0.19	2.36±0.19
1		5.07±0.14	5.73±0.14
1.5		8.32±0.35	8.26±0.35
2		11.27±1.25	11.75±1.25
2.5	Phosphate Buffer pH 7.4	8.84±0.35	20.11±0.35
3		22.34±1.06	33.61±1.06
4		34.00±0.13	45.27±0.13
5		43.44±1.26	54.71±1.26
6		56.99±0.73	68.26±0.73
7		61.70±0.48	72.97±0.48
8		70.53±0.92	81.8±0.92
9		76.03±1.41	87.3±1.41
10		80.88±0.42	92.15±0.42
11		84.71±0.56	95.98±0.56

*****All values are expressed as mean ±SD, n=3.

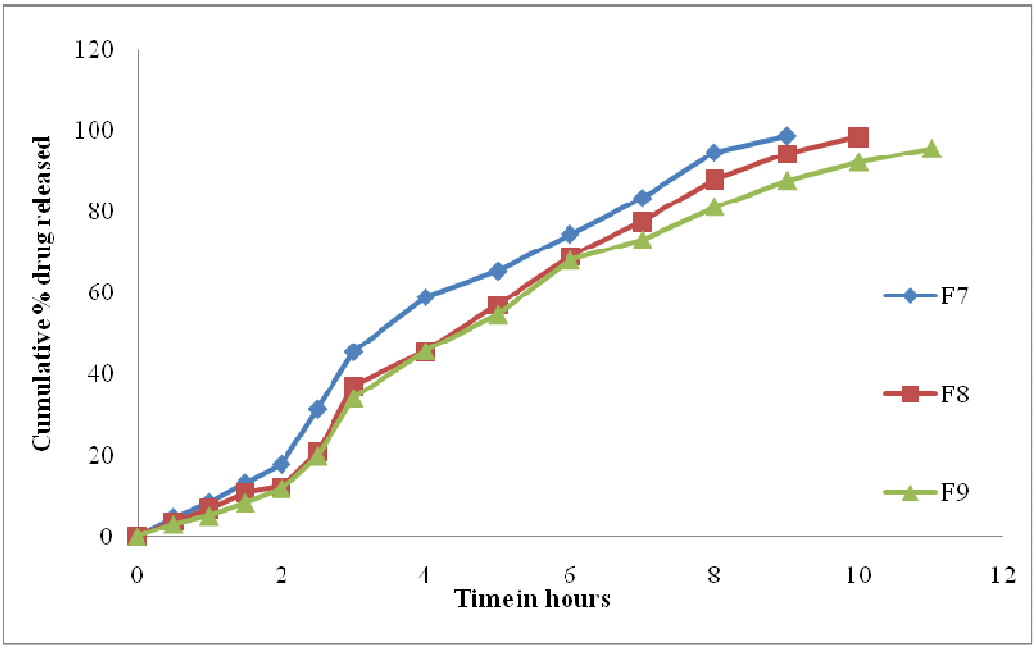


Figure 36: *In-vitro* Drug Released profile curve of formulations F7 to F9

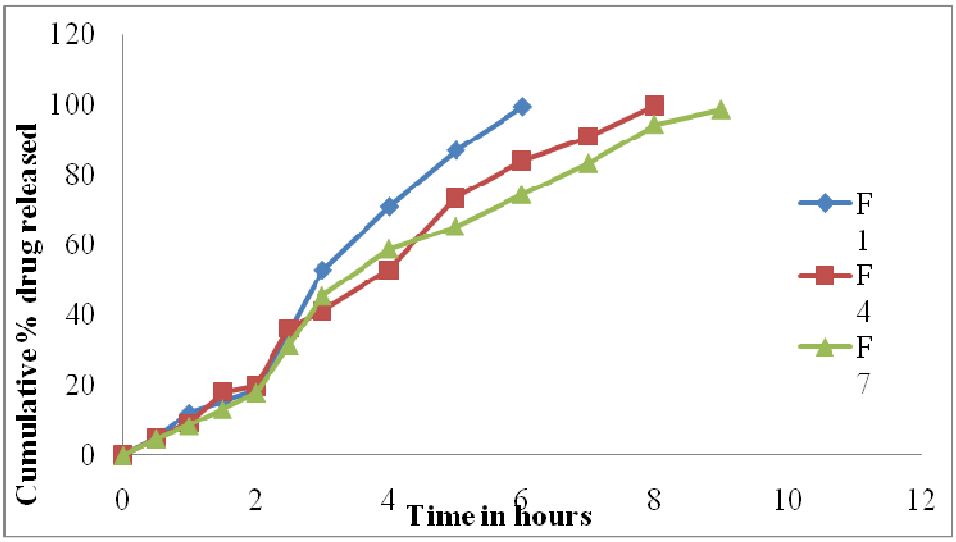


Figure 37: *In-vitro* drug released profile curve for formulations F1, F4, andF7

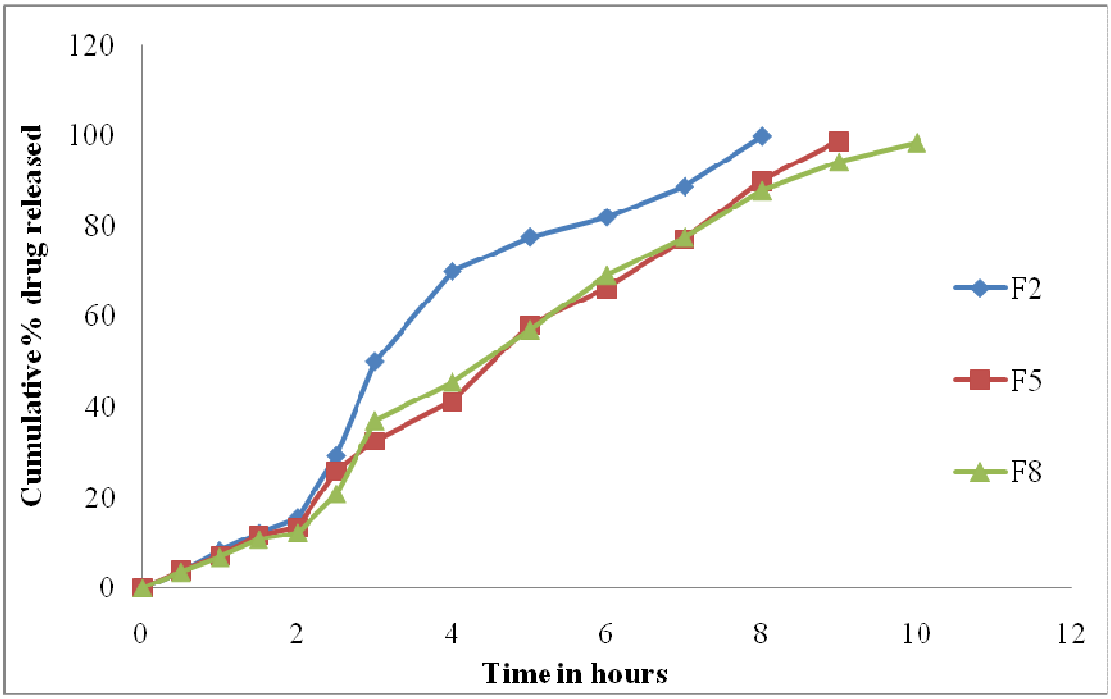


Figure 38: *In-vitro* drug released profile curve for formulations F2, F5, and F8

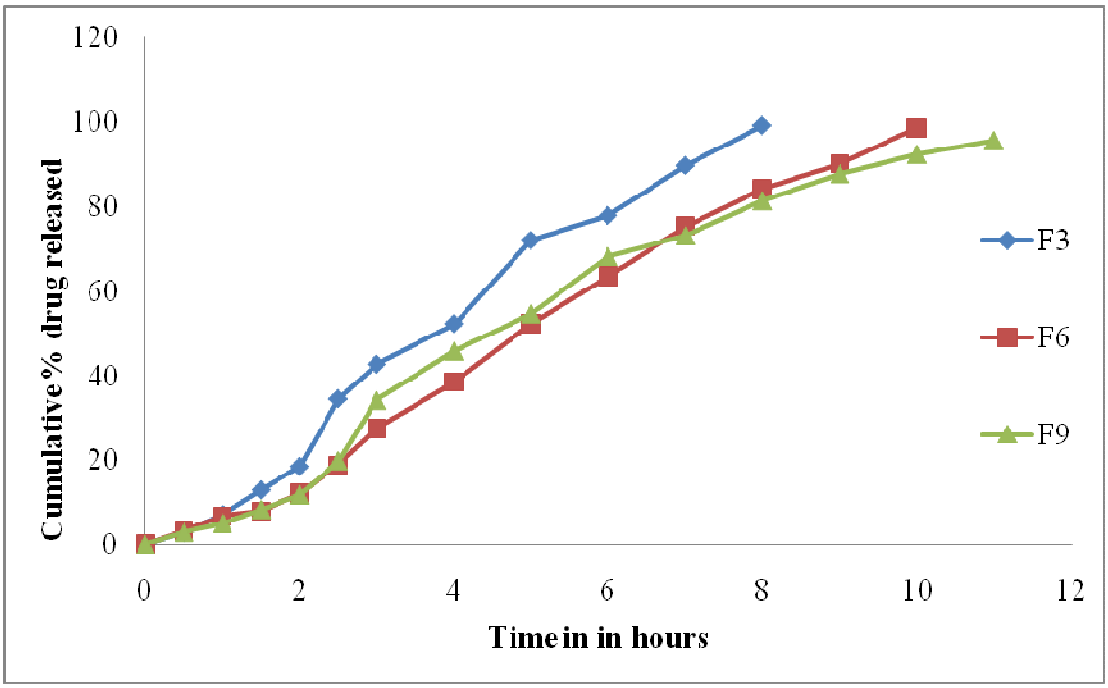


Figure 39: *In-vitro* drug released profile curve for formulations F3, F6, and F9

Table 35: Comparative study of *In-vitro* drug released profile for formulations F1 to F9

Time (hr)	Dissolution Medium	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.1 N HCl	0	0	0	0	0	0	0	0	0
0.5		5.09	3.96	2.78	4.95	3.66	3.96	4.1	3.44	2.36
1		10.49	7.1	8.13	10.15	8.14	6.19	8.7	6.77	5.73
1.5		14.23	11.61	13.88	15.97	12.14	7.95	13.78	10.73	8.26
2		17.63	13.45	17.56	19.07	15.45	12.81	17.04	12.19	11.75
2.5	Phosphate Buffer pH 7.4	34.41	32.42	32.64	36.1	29.25	19.16	30.56	20.82	20.11
3		54.18	41.27	45.51	41.18	49.98	27.79	44.34	37.00	33.61
4		68.96	58.09	51.01	52.2	69.94	39.72	58.11	45.62	45.27
5		86.96	66.27	74.53	73.38	77.58	53.3	64.23	57.11	54.71
6		97.41	77.12	79.26	84.06	81.95	76.04	73.49	69.14	68.26
7		-	89.98	92.71	90.93	88.7	75.3	82.11	77.61	72.97
8		-	98.87	98.11	99.70	99.74	84.16	93.31	87.91	81.8
9		-	-	-	-	-	90.71	97.35	94.25	87.3
10		-	-	-	-	-	99.31	-	98.50	92.15
11		-	-	-	-	-	-	-	-	95.98

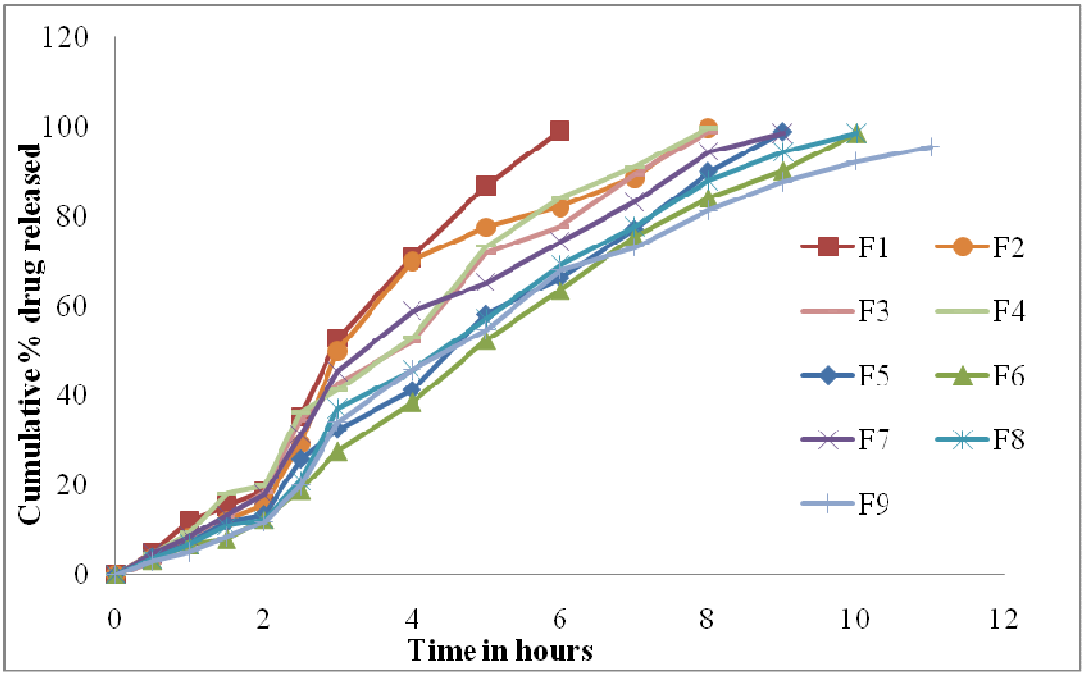


Figure 40: Comparative study of *In-vitro* drug released curve of formulations F1 *to* F9

Acyclovir is a water insoluble drug; its release from the matrix is largely dependent on the polymer swelling, drug diffusion and matrix erosion. The concentration of polymer in the sustained release layer was a key factor in controlling the drug release. Various sustained release formulations were formulated with Xanthan gum, Sodium Alginate and Chitosan polymer alone; polyvinyl pyrolidone as binder and lactose was used as diluents, Magnesium stearate as a Lubricant.

In vitro release studies of formulations **F1, F2 and F3** prepared by Xanthan gum with concentrations of 10%, 20%& 30% respectively, in which the release rate of F1 was found to be 97.41±1.01, at the 6^{th} hour and for 98.87±1.26 F2 at the end of 8^{th} hour and 98.11±0.95 for F3 at the end of 8^{th} hour. The drug release rate was found to be slower when increasing the concentration of polymer (Xanthan gum).

In vitro release studies of formulations **F4, F5 and F6** prepared by Sodium Alginate with concentrations of 10%, 20%& 30% respectively, in which the release rate of F4 was found to be 99.70±0.48, at the 8^{th} hour and for 99.74±0.05 F5 at the end of 8^{th} hour and 99.31±4.74 for F6 at the end of 10^{th} hour. The release rate was found to be retarded increasing in the concentration of polymer (Sodium Alginate).

In vitro release studies of formulations **F7, F8 and F9** prepared by Chitosan with concentrations of 10%, 20% & 30% respectively, in which the release rate of F7 was found to be 97.35±0.87, at the 9^{th} hour and for 98.50±0.91 F8 at the end of 10^{th} hour and 95.98±0.56 for F9 at the end of 11^{th} hour. The release rate was found to be sustained due to increased in the concentration of polymer (Chitosan).

In vitro release studies of formulations **F3, F6 and F9** prepared by with concentrations of 30% Xanthan gum, Sodium Alginate and Chitosan shows sustained release effect of F3 formulation 98.11±0.95 at the end of 8^{th} hour 99.31±4.74 for F6 at the end of 10^{th} hour and 95.98±0.56 for F9 at the end of 11^{th} hour.

From the above evaluation parameters it was concluded that the formulation F9 having a high percentage of drug release in a sustained manner, so the formulation F9 was selected as the optimized formulation. Hence the formulation F9 was selected for the further stability study.

i) Data Analysis (Curve Fitting Analysis)

Korsemeyer-Peppas model indicates that the release mechanism is not well known or more than one type of release phenomena could be involved. The 'n' value could be used to characterize different release mechanisms as:

Table 36: Different drug release mechanisms of kinetic model

Release exponent (n)	Drug Transport Mechanism
0.5	Fickian diffusion (Higuchi Matrix)
0.45< n=0.89	Non- Fickian diffusion
0.89	Case II transport
Higher than 0.89	Super case II transport

It ranges between 0.5 to 1, so it was concluded that the drug release occurred via non-fickian diffusion, which shows that the release from initially dry, hydrophilic glassy polymers that swell when added to water and become rubbery show anomalous diffusion as a result of the rearrangement of macro molecular chains.

7.3 Kinetic studies

Table 37: In-vitro Release Kinetic models for Acyclovir sustained release Matrix tablets of formulations (F1 to F9)

Code	Zero order		First order		Higuchi		Korsemeyer-Peppas		Best fit model
	R^2	K_0 (mg/h^{-1})	R^2	K_1 (h^{-1})	R^2	K ($mgh^{-1/2}$)	R^2	n	
F1	0.968	12.810	0.913	0.2209	0.8775	26.432	0.9697	1.69	Zero order
F2	0.969	10.982	0.956	0.1962	0.9141	26.045	0.9072	1.31	Zero order
F3	0.985	9.801	0.931	0.1656	0.8884	22.961	0.9887	1.35	Peppas
F4	0.983	10.005	0.936	0.1708	0.8855	23.426	0.9899	1.38	Peppas
F5	0.976	8.965	0.895	0.1606	0.8646	21.989	0.9921	1.49	Peppas
F6	0.972	8.424	0.913	0.1551	0.8574	21.658	0.9716	1.73	Peppas
F7	0.988	9.288	0.955	0.1598	0.9146	23.132	0.9761	1.25	Zero order
F8	0.985	8.961	0.942	0.1682	0.8941	23.302	0.9467	1.45	Zero order
F9	0.981	8.289	0.958	0.1517	0.9113	22.672	0.9426	1.31	Zero order

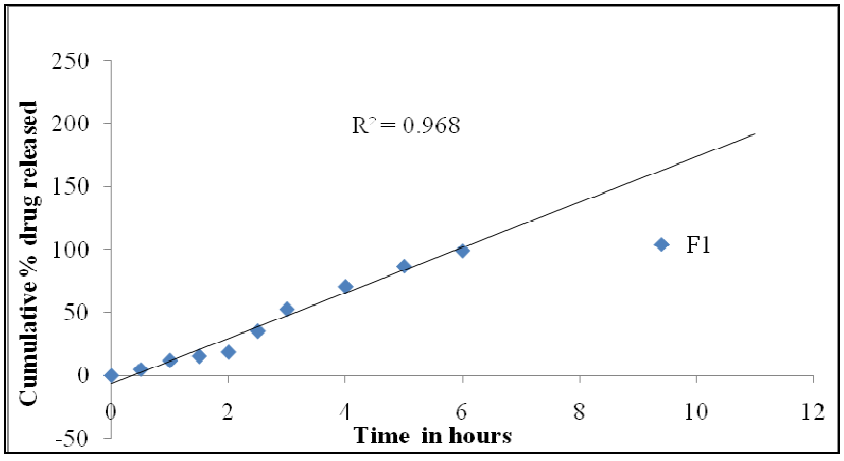


Figure 41: Best fit model (Zero) of formulation F1

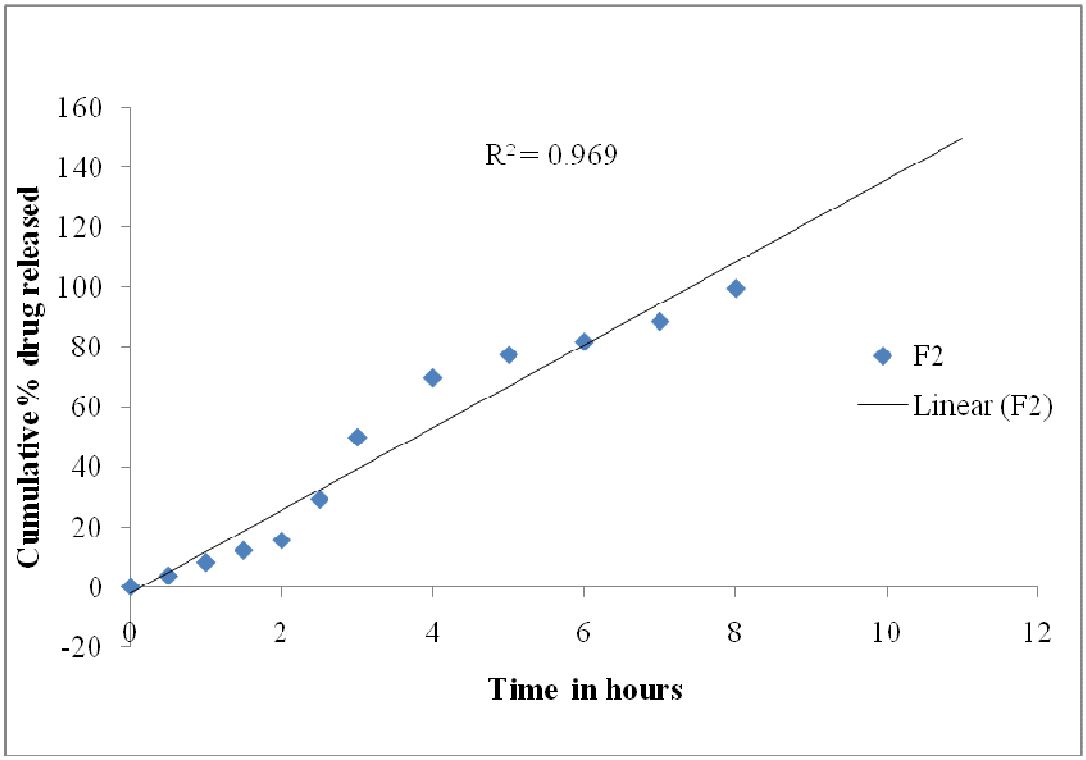


Figure 42: Best fit model (Zero) of formulation F2

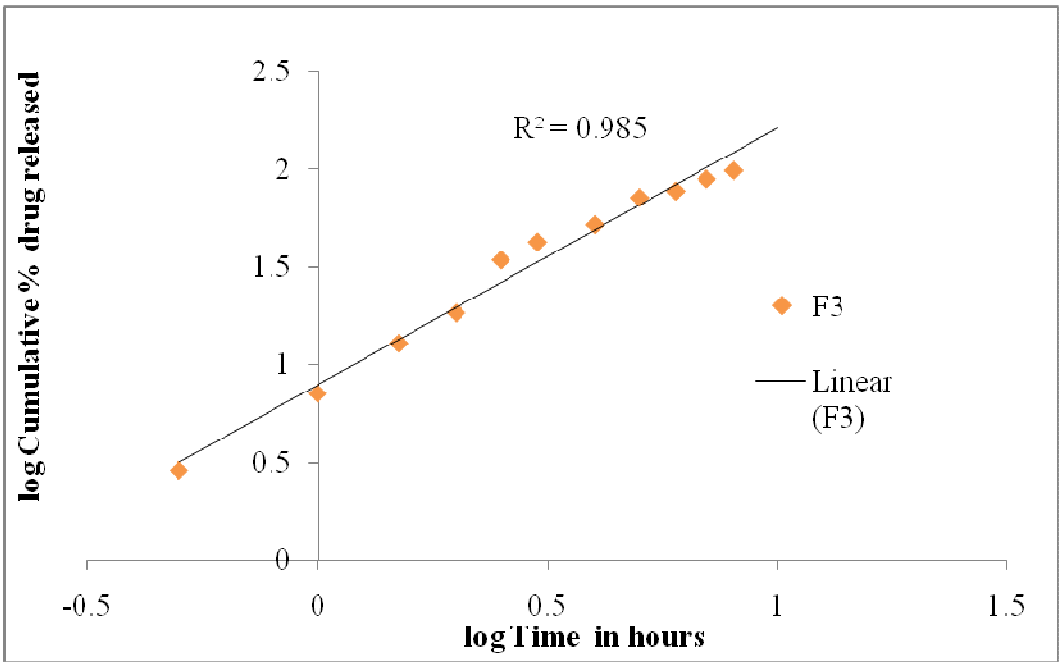


Figure 43: Best fit model (Peppas) of formulation F3

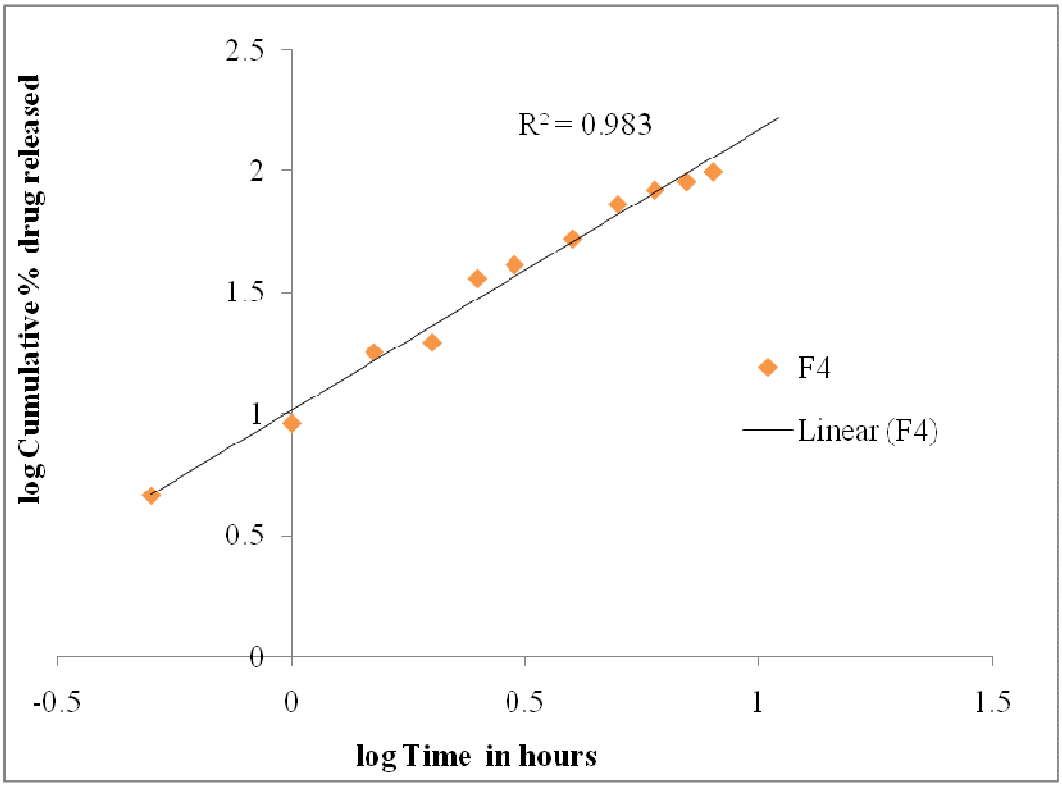


Figure 44: Best fit model (Peppas) of formulation F4

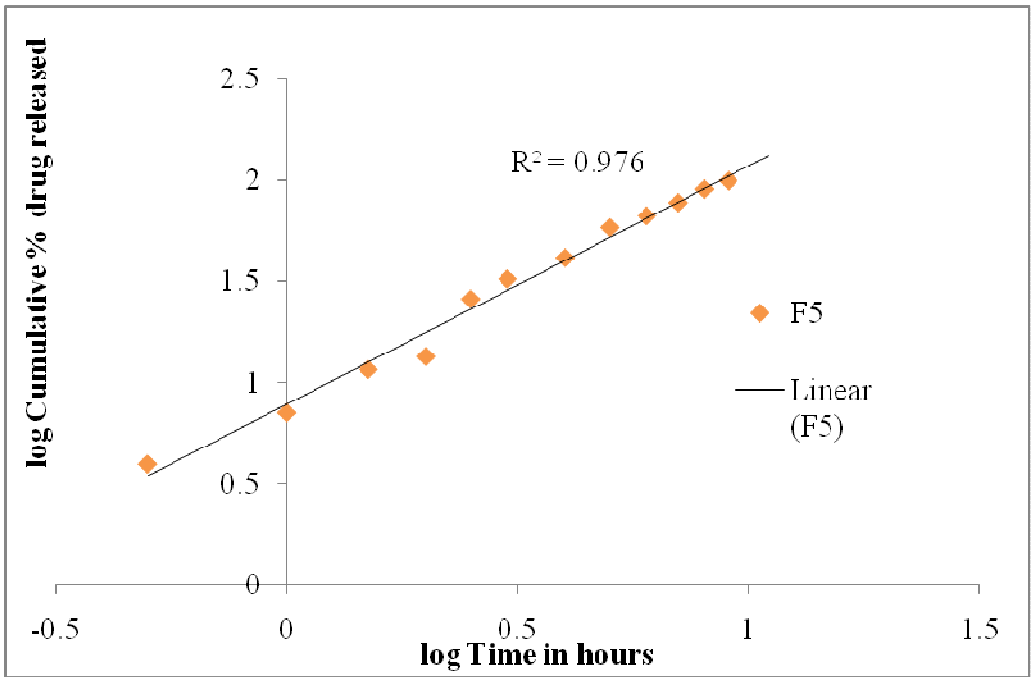


Figure 45: Best fit model (Peppas) of formulation F5

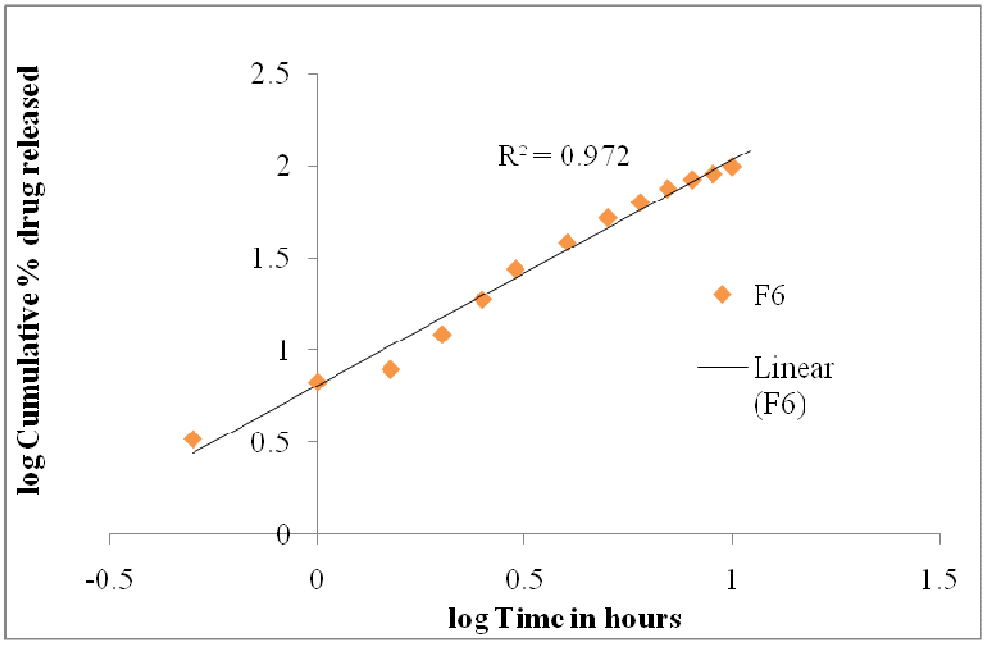


Figure 46: Best fit model (Peppas) of formulation F6

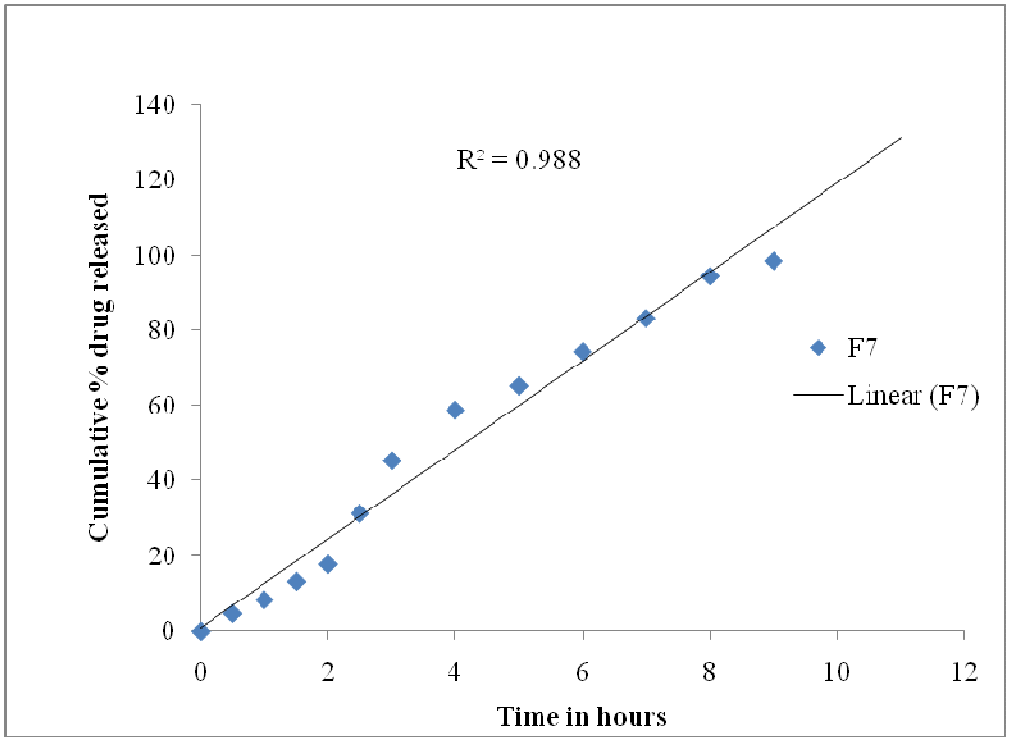


Figure 47: Best fit model (Zero) of formulation F7

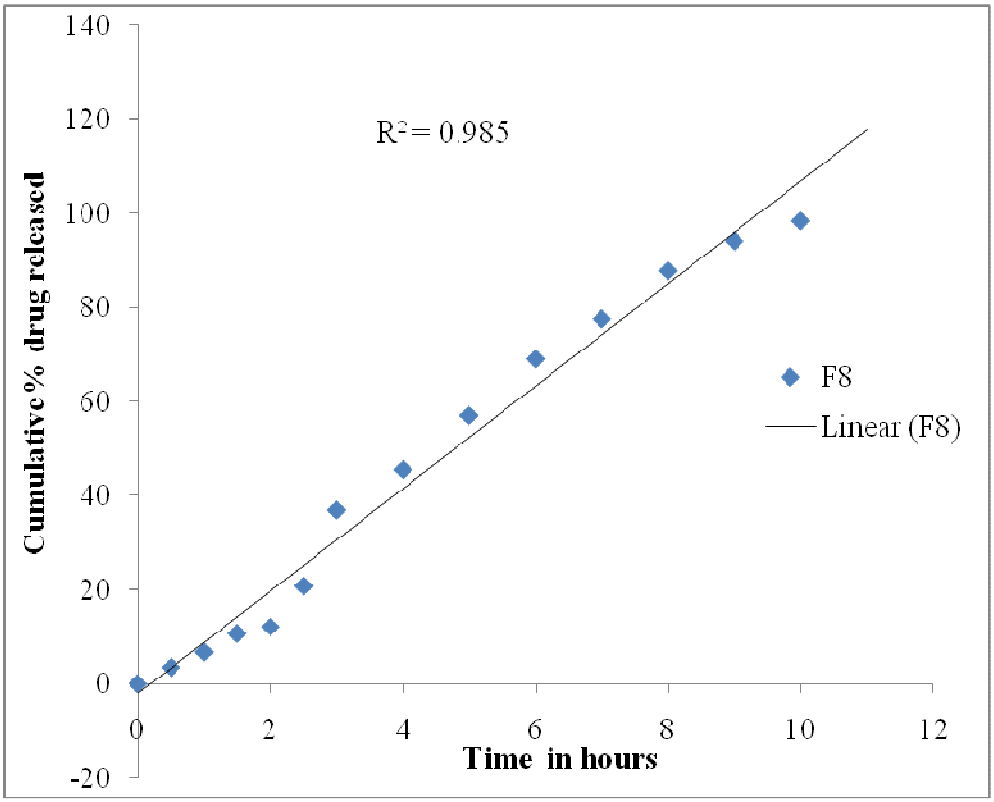


Figure 48: Best fit model (Zero) of formulation F8

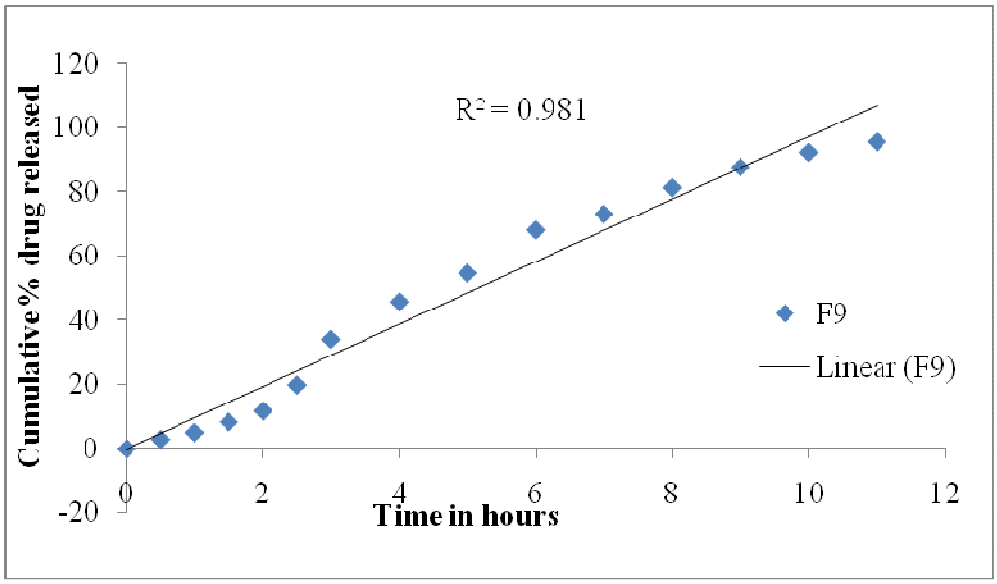


Figure 49: Best fit model (Zero) of formulation F9

To know the kinetics of the best formulations, the release data was treated according to different models. Drug release data of tablets was fitted in zero order equation (R^2= 0.9697, 0.9072, 0.9761, 0.9467, 0.9426 for F1, F2, F7, F8 and F9) and found release mechanism to be diffusion. And F3, F4, F5 and F6 are shows the Peppas (R^2=0.985, 0.983, 0.976, 0.972)

The results of dissolution data fitted to various drug release kinetic equations. Modal was found to be the best fitted in all dissolution profile having higher correlation coefficient followed by Zero order model and the Peppas release equation. The kinetic values obtained from different formulations are tabulated in table 37. Optimized formulation F9 shows the Super case II transport Mechanism

7.4. STABILITY STUDY:

After storage the formulation was analyzed for Physico- chemical parameters, results were showed in Table 25.

Table 38: Stability study of formulation F9 of sustained release Acyclovir tablets at room temperature (25^0 C ± 2^0 C / 60% RH ± 5%) and Accelerated temperature (40^0 C ± 2^0 C / 75% RH ± 5%).

Parameter	Initial	At Room temperature			At Accelerated temperature		
		1st Month	2nd Month	3rd Month	1st Month	2nd Month	3rd Month
Hardness (kg/cm^2)*	5.78± 0.37	5.70± 0.17	5.63± 0.36	5.35± 0.39	5.72± 0.040	5.60± 0.025	5.37± 0.027
Drug content (%)	100.11± 2.38	100.01± 1.65	100.00± 0.32	99.87± 0.22	100.05± 0.578	99.91± 0.375	99.76± 0.417
***In vitro* drug released at end of 11 hr**	95.98± 0.56	95.39± 0.19	95.07± 0.98	95.01± 0.68	95.62± 1.11	95.35± 0.32	95.11± 1.01

*All the values are expressed as mean± SD, n=3.

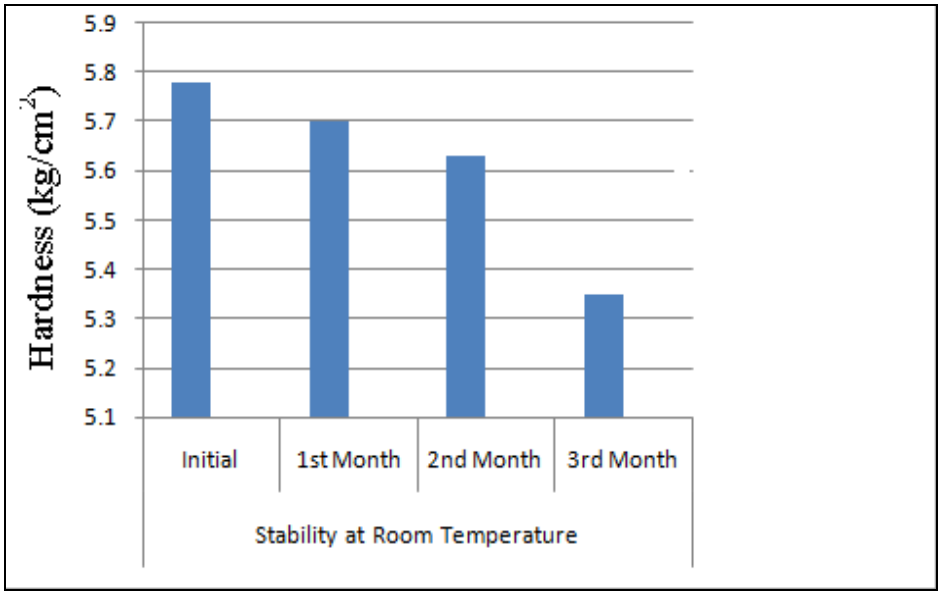


Figure 50: Comparisons of Hardness before and after stability period at room temperature (25^{0} C ± 2^{0} C / 60% RH ± 5%)

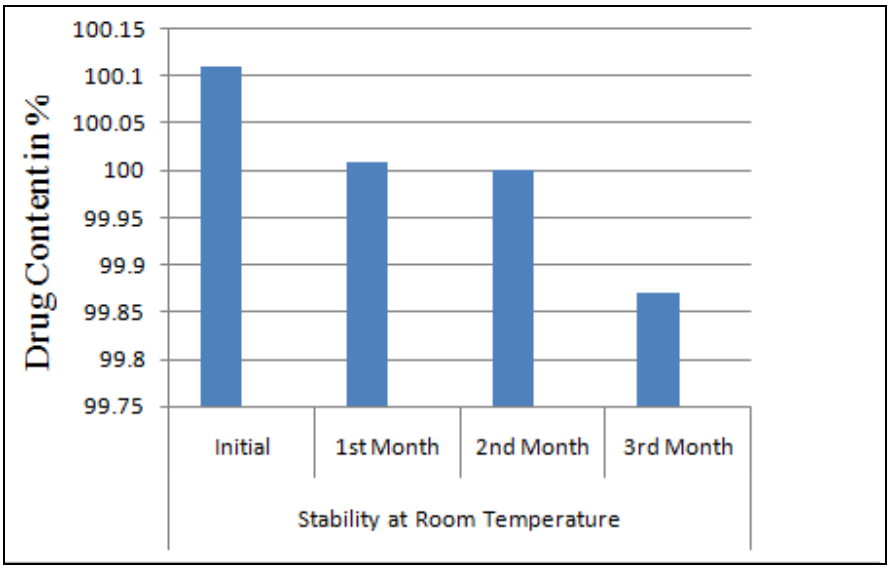


Figure 51: Comparisons of drug content before and after stability period at room temperature (25^{0} C ± 2^{0} C / 60% RH ± 5%)

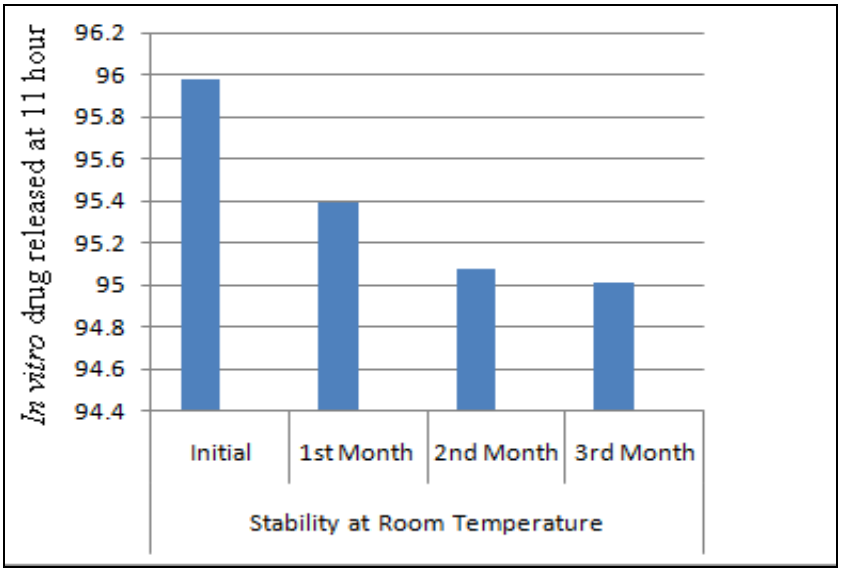


Figure 52: Comparisons of *in vitro* drug released before and after stability period at room temperature (25^{0} C ± 2^{0} C / 60% RH ± 5%).

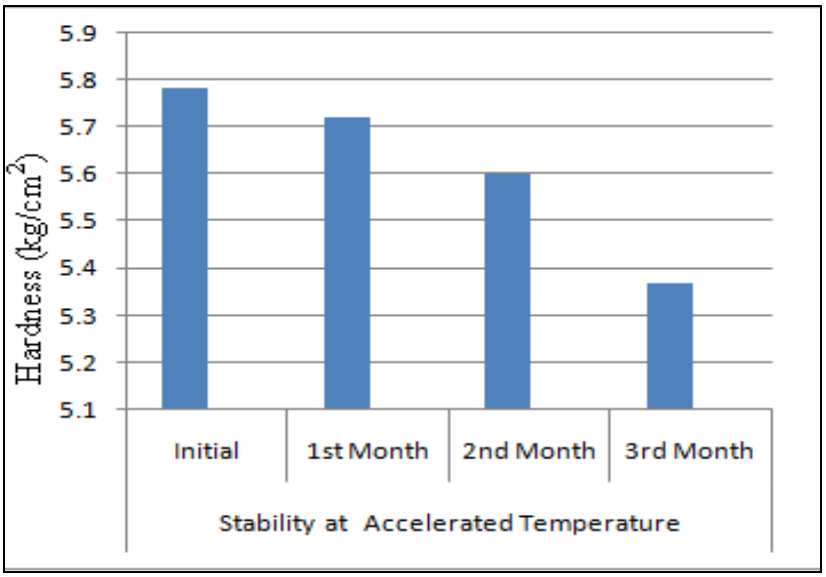


Figure 53: Comparisons of Hardness before and after stability period at Accelerated temperature (40^{0} C ± 2^{0} C / 75% RH ± 5%).

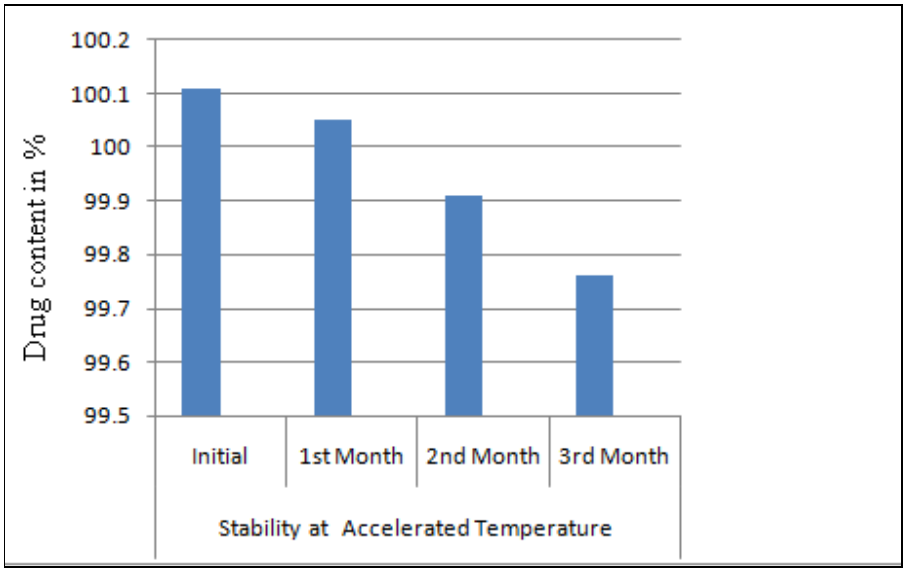


Figure 54: Comparisons of drug content before and after stability period at Accelerated temperature (40^{0} C ± 2^{0} C / 75% RH ± 5%)

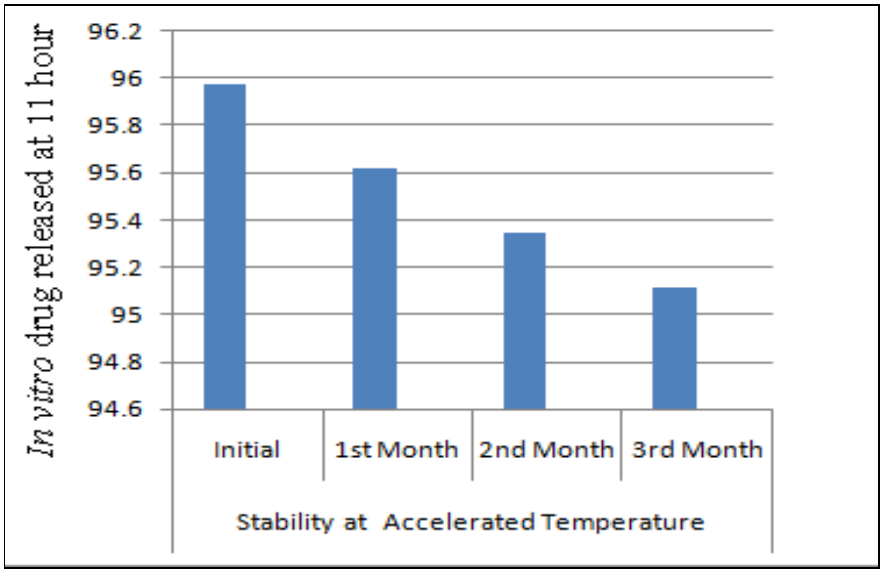


Figure 55: Comparisons of *in vitro* drug released before and after stability period at Accelerated temperature (40^{0} C ± 2^{0} C / 75% RH ± 5%)

SUMMARY AND CONCLUSION

8. SUMMARY AND CONCLUSION

In present investigation an attempt has been made to design and develop Acyclovir sustained release matrix tablets using Xanthan gum, Sodium Alginate and Chitosan, as release retarding polymers. Acyclovir is widely used as an antiviral drug; therefore have been selected to prepare sustained release dosage forms.

An ideal matrix formulation prepared with different polymers and diluents concentrations should release its content in a sustained profile a reasonable length of time and preferably with zero order kinetic.

The active pharmaceutical ingredient Acyclovir was evaluated for its physical characteristics, analytical profiles and drug polymer compatibility study. The powder blend was prepared by mixing all ingredients in mortar and pestle. The prepared powder blend was evaluated for Angle of repose, Bulk density, Tapped density and Carr's index. The results obtained were found to be satisfactory and within the specified limits.

Acyclovir sustained release tablet was prepared by using direct compression method and an active medicament, polymer and lubricant concentrations were optimized by various trials. The optimization procedures aided in the stabilization of the formula. After compression the following parameters of Thickness, Hardness, Weight variation, Friability, content uniformity and *In-Vitro* release studies were evaluated.

Result of the present study demonstrated that hydrophilic polymers could be successfully employed for formulating sustained release matrix tablets of Acyclovir. The investigated sustained release matrix tablet was capable of maintaining constant plasma concentration up to

11 hours. This can be expected to reduced the frequency of administration and decrease the dose dependent side effects. The efficacy and safety of Acyclovir tablet dosage form are expected to offer optimum therapeutic efficacy and improved patient compliance.

In the present study the effect of types and concentration of polymer were studied on *In-Vitro* drug release. It shows that increase in concentration of polymer results in the sustained drug released at 11 hours. The study has revealed that by increasing concentration of polymer, release rate of drug was retarded and results confirmed that the released rate from hydrophilic matrix tablets depends on type and concentration of polymer.

In present studies, matrix formulation containing Chitosan was probably showed better drug released up to 95.98 % within 11 hours, which was the average gastrointestinal residence time.

According to stability study it was found that there was no significant change in hardness, drug content and *in vitro* dissolution of optimized formulation (F9). So the formulation F9 was concluded best formulation among the formulations F1 to F9 were prepared

FUTURE PROSPECTS

9.FUTURE PROJECTS

The study requires attention of researcher to develop sustained drug delivery systems using other hydrophilic polymers. Furthermore, the study can be extended to evaluate *in-vivo* performance and also *In-vitro-In-vivo* correlation of the tablet.

This dosage forms holds promise for further systems. *In-vitro-In-vivo* correlation (IVIVC) will serve as a means of modeling the human organism and of gaining a better understanding of drug absorption and its dependence on in vitro release process.

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